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# PHOSPHORUS-CONTAINING DERIVATIVES OF INDOLE AND PYRROLE. (REVIEW)

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*Data on the synthesis and chemical properties of the phosphorus-containing derivatives of indoles and pyrroles, published in 1976-1998, are reviewed. The introduction of substituents containing tri- and tetracoordinated phosphorus atom into the heterocycle and the side chain is discussed. Information on the biological activity is presented.*

**Keywords:** indole, pyrrole, phosphorylation.

Indole can be called quite rightly a unique compound, and it can be stated confidently that no other substance has been the subject of so many publications [1-4]. The indole system is present in many biologically important compounds. As examples it is possible to mention the irreplaceable amino acid tryptophan, the growth-regulating substance heteroauxin (indolylacetic acid), one of the mediators in the transmission of nerve impulses (serotonin), a large group of indole alkaloids, and a series of antibiotics (e.g., indolmycin, pimrin). Indole preparations obtained synthetically and possessing a varied range of activity are widely used in medical practice: mexamin (for the prevention of radiation sickness), indopan (antidepressant), indomethacin (anti-inflammatory), and others.

The high biological activity of organophosphorus compounds, among which highly active pesticides, compounds with anticholine esterase activity, compounds with antiviral and antimicrobial activity, and war gases have been found, is well known. It is natural to suppose that the combination of indole and phosphorus fragments in one molecule will make it possible to expect phosphorus-containing indoles to exhibit specific useful characteristics, particularly at the level of biological activity. An example of such a combination is the natural compound psilocybin (dimethyltryptamine 4-phosphate), which is the active principle of *Mexican mushrooms* with strong hallucinogenic activity [5].

The synthesis of indoles by the Fischer method has been the subject of a review, where phosphorus trichloride and polyphosphoric acid were used as cyclizing agents [6]. Although the first publication on the synthesis of phosphorus-containing indoles appeared in 1930 [7], reviews on this subject are few. The treatment of the subject in [8] was fragmentary, while the review [9] covered the literature up to 1975. It is also possible to mention [10], which was devoted to the phosphorylation of pyrrole and its carbonyl derivatives.

The present review is timely in the light of the foregoing and covers publications from 1976 to 1998. The material is arranged according to the nature of the agent that phosphorylates indole and pyrrole.

## 1. PHOSPHORYLATION WITH P(III) ACID CHLORIDES

### 1.1. Phosphorylation of Indole in the Pyrrole Part of the Molecule

Indole (**1**) has two reaction centers (the $C_{(3)}$ atom and the NH group) at which attack by the P(III) acid chlorides can occur. Quantum-chemical calculations [11] on model reactions show that from the standpoint of MO

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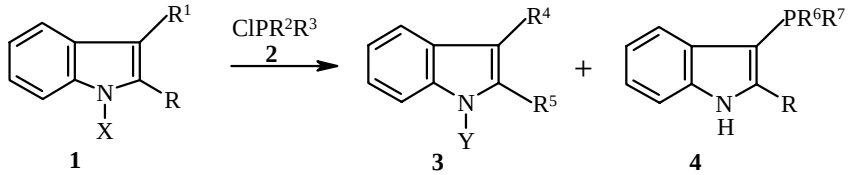
perturbation theory N-phosphorylation is favorable in all cases, but for the chlorophosphites phosphorylation at position 3 is preferred thermodynamically. As shown by experiments [12-15], monochlorides of P(III) acids **2** form the N-phosphorylated derivatives **3** preferentially with indole. Only in the case of O,O-dialkyl chlorophosphites the products from $C_{(3)}$-phosphorylation **4** were detected:

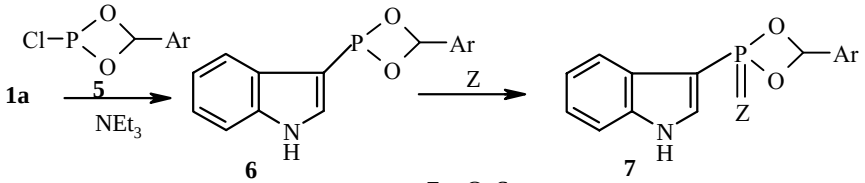



**1** **3** **4**

**1a** X = R = $R^1$ = H; **1b** X = R = H; $R^1$ = Me; **1c** X = $R^1$ = H; R = Me; **1d** X = MgI; R = $R^1$ = H;
**1e** X = Me; R = Li; $R^1$ = H. **2a** $R^2$ = $R^3$ = OAlk; **2b** $R^2$ = OAlk; $R^3$ = $NAlk_2$; **2c** $R^2$ = $R^3$ = $NAlk_2$.
**3a** Y = $P(OAlk)_2$; $R^4$ = $R^5$= H; **3b** Y = $P(OAlk)_2$; $R^4$ = Me; $R^5$ = H; **3c** Y = P(OAlk)$NAlk_2$;
$R^4$ = $R^5$ = H; **3d** Y = $P(NAlk_2)_2$; $R^4$ = $R^5$ = H; **3e** Y= Me, $R^4$ = H, $R^5$ = $P(NAlk_2)_2$.
**4a** $R^6$ = $R^7$ = OAlk; R = H; **4b** $R^6$ = $R^7$ = Ph; R = H

The C-phosphorylation of alkylindoles was realized using the magnesium and lithium derivatives of indole. The $C_{(2)}$-substituted compound **3e** was obtained from 2-lithio-1-methylindole (**1e**), and the $C_{(3)}$-substituted compounds **4a**,**b** were obtained by means of the indole Grignard reagent **1d** [11, 16, 17]. It was shown [17] that 3-indolylphosphonite **4b** forms complexes with copper(I) halides.

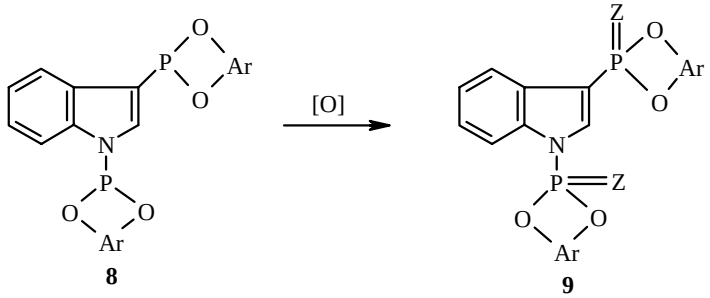
The reaction of indole with pyrocatechol chlorophosphite (**5**), in which the electrophilicity of the phosphorus atom is higher than in dialkyl chlorophosphites, leading to an increase in the proportion of $C_{(3)}$-phosphorylated compounds, was studied in order to explain the effect of the environment of the P(III) atom on the direction of phosphorylation [18]. In fact, according to the $^{31}P$ NMR data, the reaction product **6** gives only one signal with a chemical shift of 128 ppm, indicating reaction at position 3:




**6** **7**

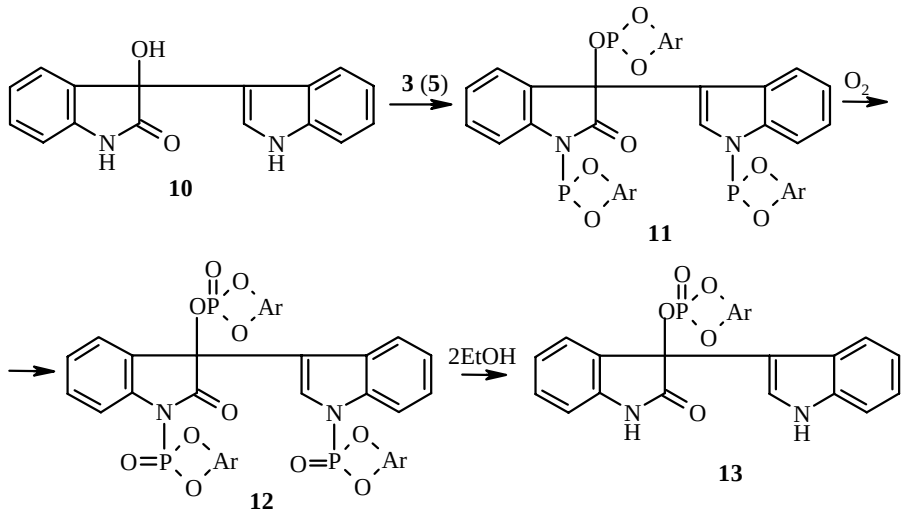
Z = O, S

Since the P(III)-containing indoles **6** are unstable, they are converted into indoles **7** containing a tetracoordinated phosphorus atom. The use of twice the amount (instead of an equimolar amount) of the reagent **5** makes it possible to obtain 1,3-di[phosphito(phosphonito)]indoles **8**, which are oxidized to the corresponding P(V) derivatives **9** for stabilization.



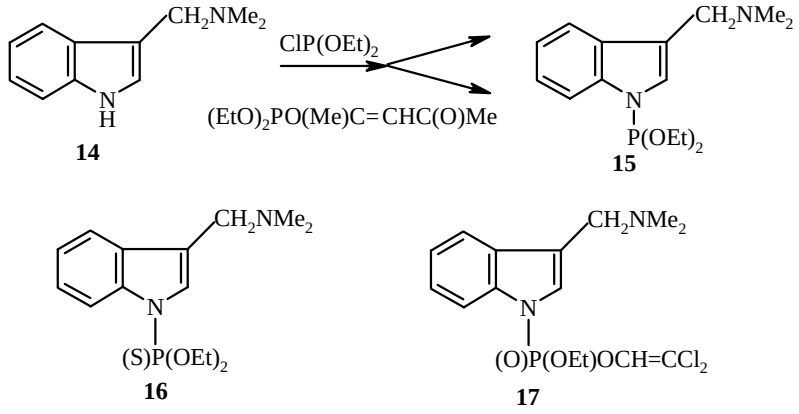

**8** **9**

In the same paper [18] compound **5** was used for the phosphorylation of 3-hydroxy-3-(3-indolyl)-2-indolinone (**10**). The triphosphorylated compound **11** that forms is oxidized to the corresponding triphosphate **12**; alcoholysis of compound **12** with 2 moles of ethanol leads to monophosphate **13**, which is also produced in an alternative synthesis from compounds **10** and **5** (in a ratio of 1:1) followed by oxidation of the reaction mass:



According to $^{31}P$ NMR spectroscopy, the reaction of carbazole, 2,3-dimethylindole, and 2,3-diphenylindole with compound **5** leads to the products from N-phosphorylation (140, 142, and 141 ppm respectively).

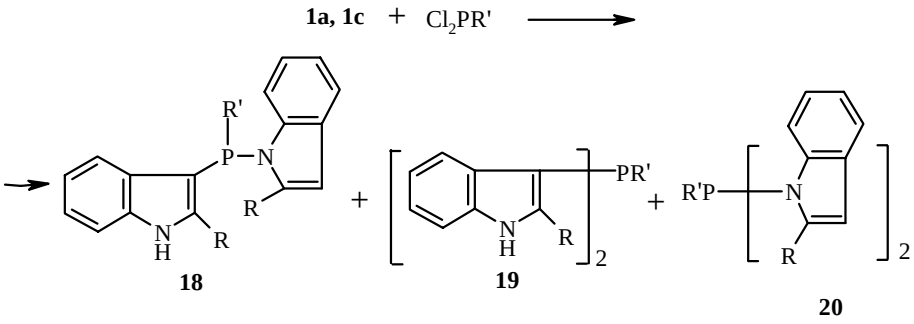
Gramine – 3-(dimethylaminomethyl)indole (**14**) – is a readily obtainable derivative of indole and is produced with a quantitative yield by the Mannich reaction. In [19] it was phosphorylated with diethyl chlorophosphite. 3-(Dimethylaminomethyl)-1-(triethoxyphosphito)indole (**15**) was obtained also by the method in [20] using diethyl penten-3-on-2-yl phosphite. Compound **15** readily adds sulfur with the formation of the corresponding gramine 1-thiophosphate **16** and reacts with chloral according to the scheme of the Perkow reaction, forming phosphate **17**:



The phosphorylation of potassiopyrrole by the chlorides of phosphorous acid shows [21] that the process is selective and leads to the products from N-phosphorylation. The reaction of 2,4-dimethyl- and 2,3,5-trimethylpyrroles with chlorophosphites makes it possible to obtain mono- and diphosphorylated alkylpyrroles, depending on the ratio of the phosphorylating agent and alkylpyrrole [22, 23].

A special place in the series of phosphorylation reactions of pyrroles is occupied by the syntheses of phospholane structures containing pyrrole ring as substituent at the phosphorus atom. These compounds, obtained from potassiopyrrole and cyclic chlorophosphites, are convenient subjects for the study of transamidation, alcoholysis, etc. [24].

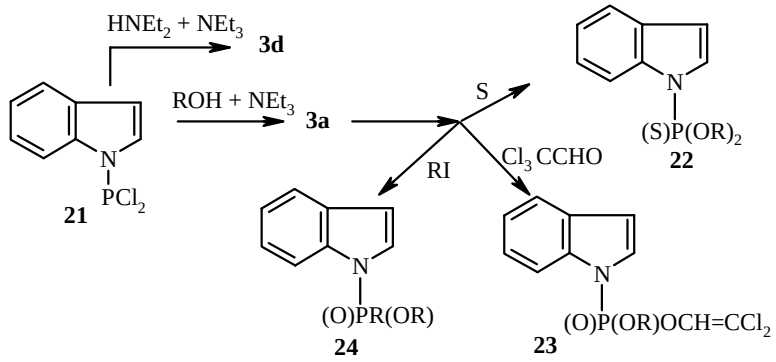
In the case of P(III) acid dichlorides, in which the electrophilicity of the phosphorus atom is increased in comparison with that of monochlorides, a decrease in the selectivity of N-phosphorylation must be expected. In fact, the reactions of indole and 2-methylindole with dichloroamidophosphites, dichlorophosphites, and dichlorophosphines lead to bisindolylphosphonites, bisindolylphosphines, and bisindolylphosphinites **18**-**20** [11, 12].




The formation of compounds **18**-**20** is explained by a two-stage process, where the intermediate product of the reaction (in the case of the reaction with phenyldichlorophosphine) is 3-indolylphenylchlorophosphine, which does not manage to accumulate in significant amounts in the reaction process and is not therefore detected in the $^{31}$P NMR spectrum.

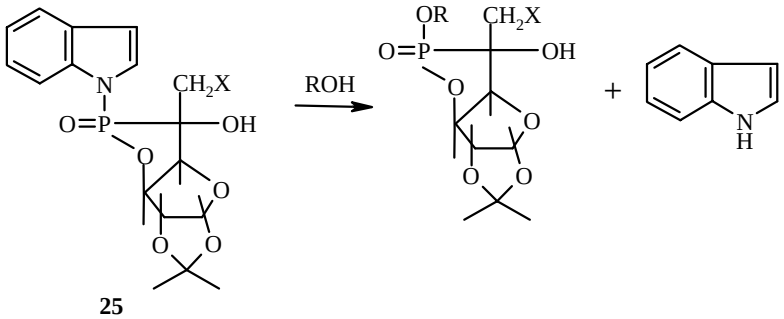
In 1992 indole was reacted with phosphorus trichloride in petroleum ether solution in the presence of triethylamine (as hydrogen chloride acceptor) with the formation of indolyldichlorophosphite **21** (yield 35%, 145 ppm) [19, 25].

Phosphite **21** is a convenient synthon for the production of various indoles containing substituents with tri- and tetracoordinated phosphorus atom **3a**,**d** and P(IV) **22**-**24**:

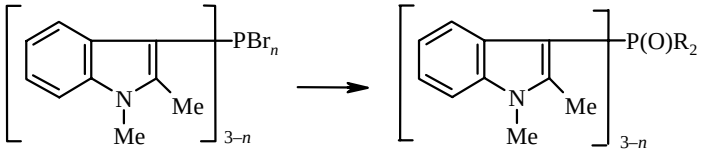



Since the P–N bond in amidophosphites **3a**,**d** readily undergoes alcoholysis [157], this process was used for the regeneration of indole from 1-phosphitoindole **3a** (R = Et, 126 ppm) by heating (140-150°C) with an excess of ethanol (ratio 1:3) in a sealed ampoule [19]. Triethyl phosphite (140 ppm) was found in the reaction mixture.

It was demonstrated [27] that the P–N bond (of the indole fragment) in the product of the reaction of indole with phosphorylated glucofuranose could be cleaved by the treatment of compound **25** with saturated alcohols:



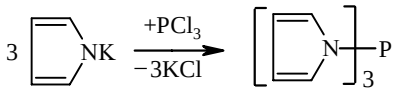

1,2-Dimethylindole readily forms phosphines **26** and 3-(1,2-dimethylindolyl)diphenylphosphine **27** in reaction with phosphorus tribromide or diphenylchlorophosphine in the presence of triethylamine. The formed phosphines without isolation from the reaction mixture are transformed into derivatives containing tetracoordinated phosphorus atom **28** [28].



**26** **28a,b**

**28 a** R = $NEt_2$, **b** R = Ph

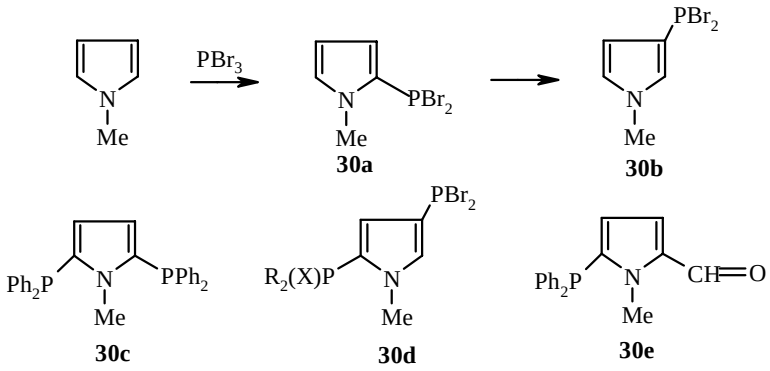
In the opinion of the authors in [10], one of the first reactions in the synthesis of phosphorylated pyrroles (the reaction of potassiopyrrole with phosphorus trichloride) leads to tris(2-pyrrolyl)phosphine, from which the corresponding thioxide and a complex with copper(I) chloride were obtained. However, the authors of [21] repeated the transformations and on the basis of a study of the $^{13}C$ NMR spectra came to the conclusion that tris(N-pyrryl)amidophosphite (**29**) is formed in this reaction:



**29**

It should be noted that amidophosphite **29** is liable to undergo a spontaneous profound transformation right down to complete resinification.

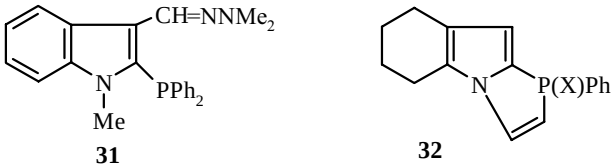
Various phosphorus-containing derivatives of 1-methylpyrrole (**30a-e**) are produced in the reaction with phosphorus tribromide [30-32, 231, 232], and the phosphorotropic rearrangement (**30a** → **30b**), occurring in methylene chloride at room temperature, was discovered:



**30a** **30b**

**30c** **30d** **30e**

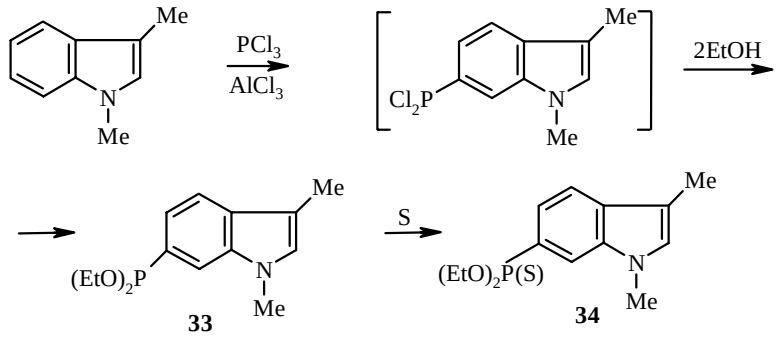
Data on the N-phosphorylated derivatives of pyrrole have been reported [29], and the synthesis of 1-methyl-2-diphenylphosphinyl-3-formylindole dimethylhydrazone **31** and tetrahydroindole derivative **32** has also been mentioned [30]:



**31** **32**

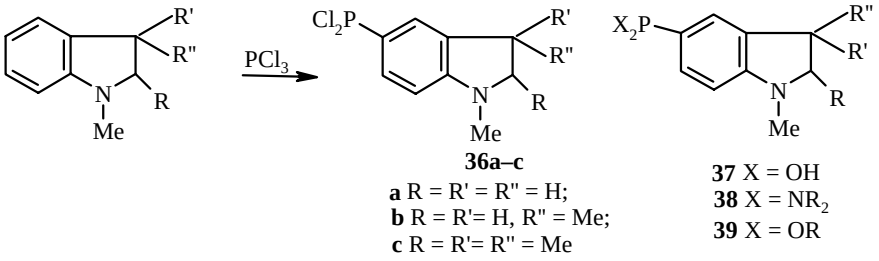
## 1.2. Phosphorylation of Indole in the Benzene Part of the Molecule

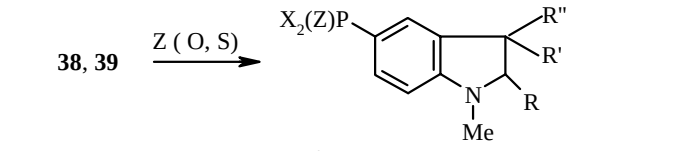
1,3-Dimethylindole reacts with phosphorus trichloride in the presence of aluminum chloride at 100-120°C with the formation of 6-dichlorophosphinyl-1,3-dimethylindole, which is esterified without isolation from the reaction mixture to indolylphosphonite (**33**) and is converted into thiophosphonate (**34**) [33-35]:

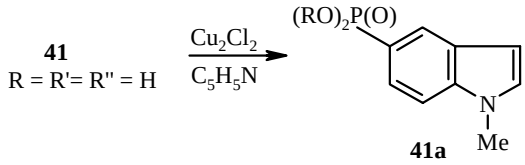


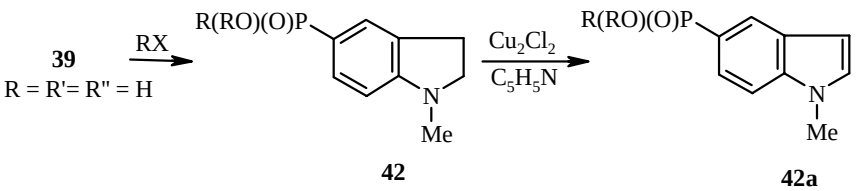
The reaction of 1,2,3-trimethylindole with phosphorus trichloride (aluminum chloride, 100-120°C, 6 h) followed by treatment of the reaction mixture with water gives 35% yield of 1,2,3-trimethyl-6-phosphonitoindole (**35**). The low yields of the products from direct phosphorylation of alkylindoles with phosphorus trichloride prompted the authors in [34, 35] to use the indoline–indole method [36, 37].

1-Methylindoline and 1,3-dimethylindoline are phosphorylated by phosphorus trichloride at 100-120°C (3 h). Here 5-dichlorophosphinylindoline **36a**,**b** is obtained from approximately half the indoline, while the other half is converted into the corresponding hydrochloride (indoline is regenerated from it by treatment with alkali) [34, 35]. With phosphorus trichloride 1,2,3,3-tetramethylindoline forms dichlorophosphine **36c** with a quantitative yield [36]. The acid chlorides **36** undergo hydrolysis (**37**), amidation (**38**), and alcoholysis (**39**). Phosphonites **38** and **39** are converted into thiophosphonates and phosphonates **40**, **41** and enter into the Arbuzov reaction (**42**) [160]:

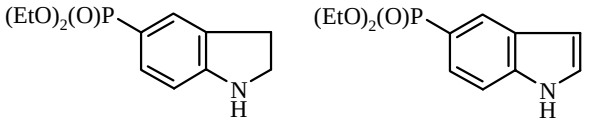






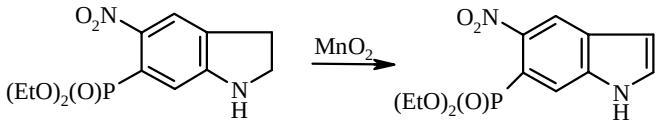


Indolines **41**, **42** are dehydrogenated by anhydrous copper chloride in pyridine to the corresponding indoles **41a**, **42a** [33, 35] with yields of up to 40%. The production of 5-(diethoxyphosphoryl)indoline (**43**) and 5-(diethoxyphosphoryl)indole (**43a**) from 5-bromoindoline (5-bromoindole) and trialkyl phosphites by the Arbuzov reaction, catalyzed by nickel chloride has been described [35]:



**43** **43a**

A method was developed [38] for the introduction of phosphoryl substituent at position 6 during the nucleophilic substitution of a nitro group in 5,6-dinitroindoline by trialkyl phosphites (dry acetonitrile, boiling). This made it possible to obtain 5-nitro-6-phosphorylindoline (**44**). The method is similar to that described for 5(6)-nitrophosphorylbenzimidazoles [39]. The dehydrogenation of indoline **44** to the corresponding 5-nitro-6-phosphorylindole **44a** can be achieved with manganese dioxide.

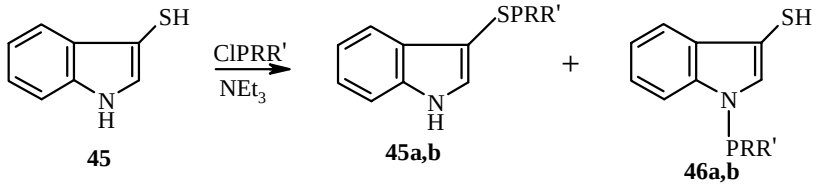


**44** **44a**

The authors of [30] have reported on the phosphorylation of 1-methylcarbazole.

### 1.3. Phosphorylation of 3-Mercaptoindole

The reaction of 3-mercaptoindole (**45**) with P(III) acid chlorides is accompanied by the formation of the S- and N-substituted isomers. The yields of the final products depend on the reaction temperature; at lower temperatures the main products are the S-derivatives **45a**,**b**, but the proportion of the N-isomers **46a**,**b** increases with increase of the temperature [11, 40, 41]:



**45** **45a,b** **46a,b**

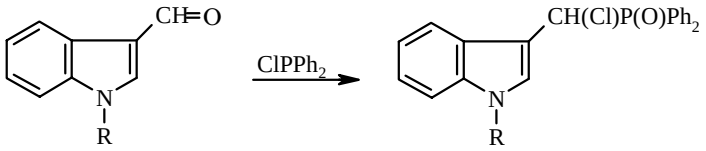
**a** R = R' = OAlk, **b** R = R' = $NAlk_2$

The reaction of 3-mercaptoindole with amidophosphite esters takes place similarly. The author of [11] has evaluated the enthalpies of the reactions at the SH and NH groups of the molecule, but the conclusions about the thermodynamically favorable reaction product need to be revised.

### 1.4. Phosphorylation of the Carbonyl Derivatives of Indole

The reaction of carbonyl compounds with P(III) acid chlorides has been widely discussed in the literature. The most complete information on this subject was compiled in the review [42]. As far as the carbonyl derivatives of indole in such reactions are concerned the information here is sparse.

Diphenylchlorophosphine reacts with 3-formylindoles **47** both at the carbonyl group and at the NH group [43], forming diphosphorylated 3-methylindole containing the phosphorus atoms in various coordinations (**48a**):



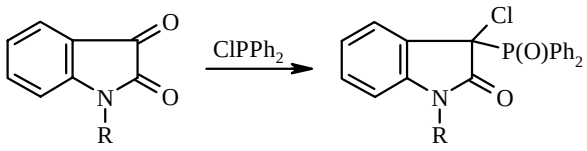

**47a,b**

**a** R = H; **b** R = Ac

**48a–c**

**a** R = $PPh_2$; **b** R = Ac; **c** R = H

The reaction of isatin **49a** and its 1-acetyl derivative **49b** with diphenylchlorophosphine leads to the phosphorylated 2-indolinones **50a**,**b** [44]:



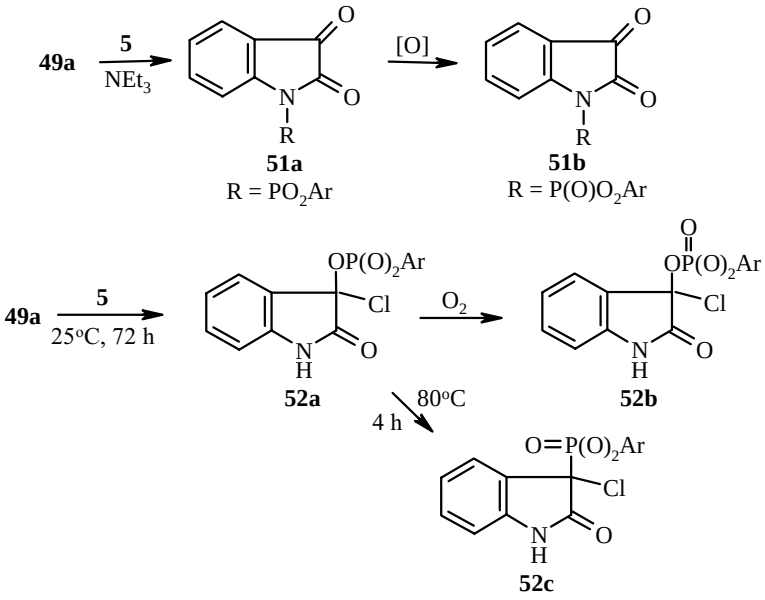

**49a**,**b**

**a** R = H; **b** R = Ac

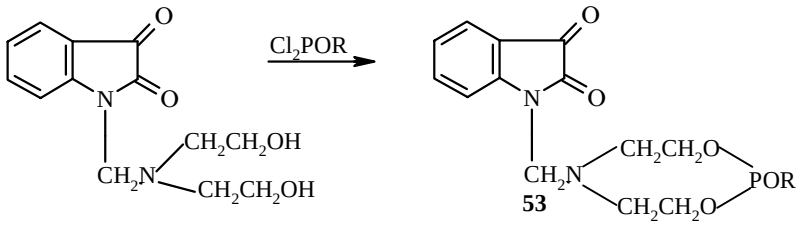
**50a**,**b**

**a** R = $PPh_2$; **b** R = Ac

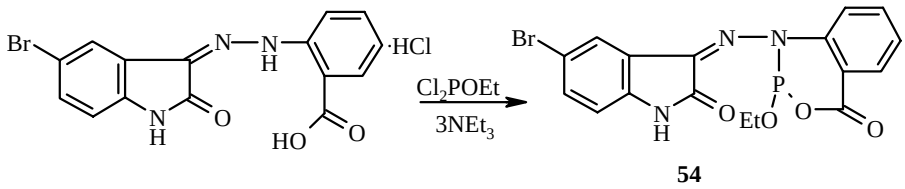
In order to determine the effect of the environment of the phosphorus atom on the direction of phosphorylation of isatin its reaction with the reagent **5** was studied [45]. At room temperature in the presence of a hydrogen chloride acceptor the reaction takes place at the NH group with the formation (according to $^{31}P$ NMR spectroscopy data) of amidophosphite **51a**, which is converted by oxidation into the more stable phosphate **51b**. In the absence of the base when the reagents are kept at room temperature for 3 days 3-chloro-3-pyrocatecholphosphito-2-indolinone (**52a**) is formed, and this is oxidized to the stable phosphate **52b**. When compound **52a** was heated in boiling benzene for 4 h in a sealed ampoule, phosphite–phosphonate rearrangement, leading to 3-chloro-3-pyrocatecholphosphonato-2-indolinone (**52c**), was detected:




The Menshutkin acid chloride was used by the author of [19] for the cyclization of isatin derivatives, and 1-[(perhydro-2-alkoxy-1,3,6,2-dioxaazophosphocin-6-yl)methyl]isatins (**53**) were obtained:



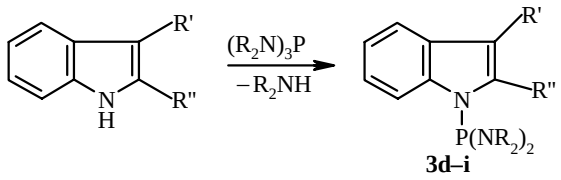
The same paper [19] reports on the phosphorylation of 5-bromoisatin *o*-carboxyphenylhydrazone hydrochloride by ethyl dichlorophosphite, resulting in the synthesis (according to the author) of 3-[N-(2-alkoxy-6-oxobenzo[*d*]-1,3,2-oxoazophosphorin-3-yl)imino]isatin (**54**):



## 2. PHOSPHORYLATION WITH ESTERS AND AMIDES OF P(III) ACIDS AND PHOSPHINES

### 2.1. Phosphorylation of Indole in the Pyrrole Fragment of the Molecule

The reaction of indoles **1a-c**, **14** with triamidophosphites and amidophosphite esters [47-49] takes place at the NH group. The reaction is carried out by heating an equimolar mixture of the reagents at 135-140°C, and the end of the process is judged from the amount of amine released, which is collected in a cooled trap. In addition, the signal at 118 ppm (triamidophosphite) in the $^{31}P$ NMR spectrum disappears, and signal for the 1-(amidophosphito)indoles (**3d-i**) appears in the region of 104-105 ppm.



**3 d** R = Et; R' =R" = H; **e** R = Bu; R' = R" =H; **f** R = Et; R' = Me; R" = H;
**g** R = Et; R' = $CH_2NMe_2$; R" = H; **h** R = Et; R' = H; R" = Me

If triamidophosphite is not specially purified it can be assumed (on the basis of published data [42, 50]) that chlorophosphites are formed initially and they then attack indole molecule at the NH bond (see the production of compound **3**).

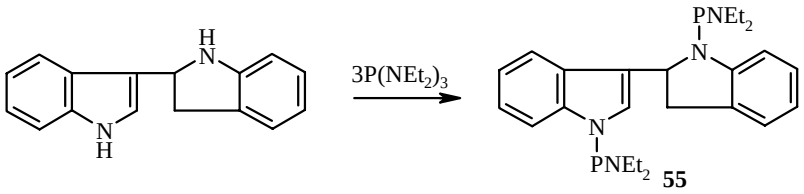
In the case of purification of triamidophosphites [51] the production of compound **3d** requires a considerable amount of time; the yields of the target compounds are increased by 10-18%. In this case, probably, the reaction takes place under the influence of the weakly acidic properties of indole. Protonation of the ambident system >P:–:N< of amidophosphite by the proton of indole clearly takes place initially with the formation of an intermediate, the dissociation of which leads to the formation of the target compound and amine.

If amidophosphite esters are used, the formation of $C_{(3)}$-substitution products with a yield of more than 30% is observed along with N-phosphorylation. The authors explain this by the catalytic effect of the amine hydrochloride impurities.

Interesting results were obtained during the reaction of indole with triamidophosphites in the presence of alcohols; trialkyl phosphite and compounds **3c**, **4c** ($R^6$ = $NAlk_2$; $R^7$ = OAlk) and **4a** were found in the reaction products, i.e., 1-3 migration of the phosphorus-containing substituent was observed.

Indole and its derivatives are acidophobic systems [55, 56], susceptible to the formation of products from dimerization and polymerization under the influence of acidic agents. This makes it possible to suppose that processes involving polymerization of phosphorus-containing indoles can occur at elevated temperatures under the influence of the acidic impurities present in amidophosphites.

The model reaction of the dimer of indole [57] with triamidophosphite (ratio 1:3) in xylene solution (130-140°C, 3.5 h, inert atmosphere) leads to compound **55**, in the $^{31}$P NMR spectrum of which the resonance signals at 104 (the indole fragment) and 98 ppm (the indoline fragment) are observed.

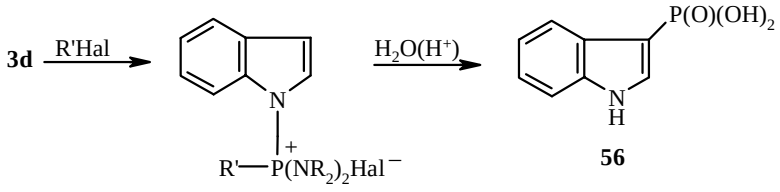



**55**

The assignment of the last signal was confirmed by an alternative synthesis of N-phosphorylated indoline (99 ppm).

Acid hydrolysis of indole **3d** with equimolar amount of water takes place with migration of the phosphorus-containing substituent. The reaction product is 3-indolylphosphonous acid (**56**). Indole is regenerated with an excess of water [49].

In the dissertation [11] amidophosphite **3d** was brought into reaction with alkyl halides. In the $^{31}$P NMR spectrum the obtained quaternary salts **57** give a signal in the region of 51-54 ppm, characteristic of a quaternized phosphorus atom. The acid hydrolysis of the salts **57** leads to the previously described [49] 3-indolylphosphonic acid (**56**).

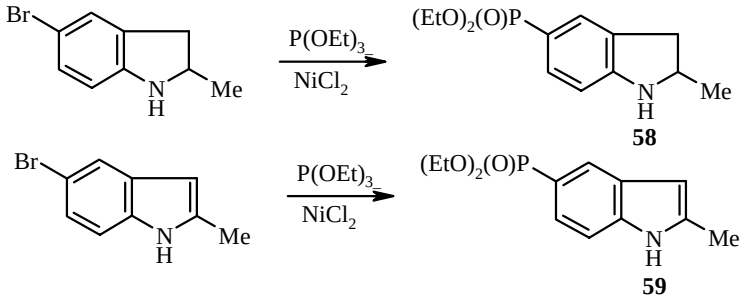



**57a–c** **56**

**57a–c** **a** R = R' = Et; **b** R = Et, R' = Pr; **c** R = R' = Bu

## 2.2. Phosphorylation of Indole and Isatin in the Benzene Fragment of the Molecule

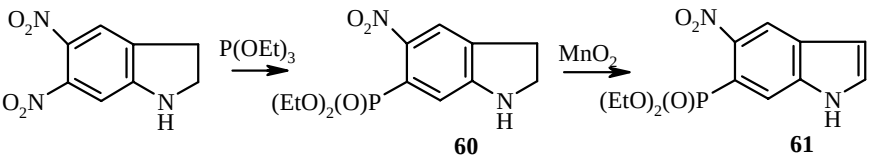
The introduction of phosphoryl fragment at position 5 of indole and indoline molecules was described in [35]. 5-Bromo-2-methylindoline reacts with an excess of phosphite, which acts as solvent and reagent, in the presence of nickel chloride, giving 5-diethoxyphosphoryl-2-methylindoline (**58**). 5-Bromo-2-methylindole reacts with triethyl phosphite in mesitylene (catalyst nickel chloride) with the formation of 5-diethoxyphosphoryl-2-methylindole (**59**):




**58**

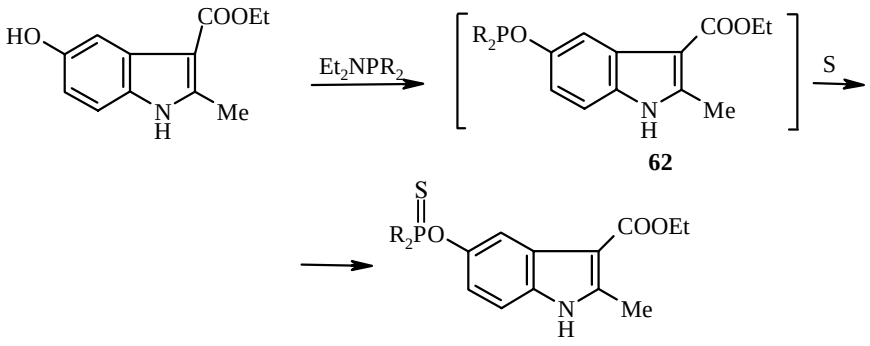
**59**

In the reaction of 5,6-dinitroindoline with trialkyl phosphite in anhydrous acetonitrile the nitro group at position 6 is substituted by phosphoryl group, which agrees with the data in [58]. 5-Nitro-6-phosphatoindoline (**60**) is formed and is dehydrogenated by manganese dioxide to 5-nitro-6-phosphonatoindole (**61**) [35]:




**60** **61**

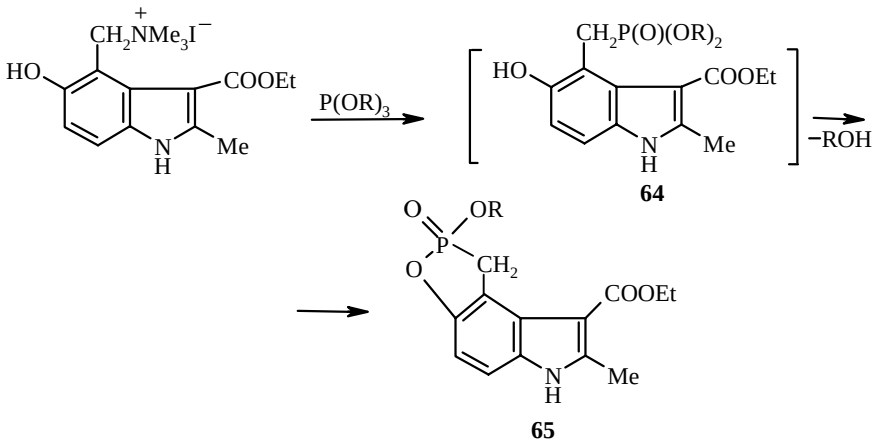
A convenient method for the production of phosphorus-containing indoles with P–O–C bond may be the reaction of hydroxyindoles with the chlorides of phosphorus acids [59, 60, 158]. 5-Hydroxyindole, obtained by the Nenitzescu reaction [160, 161], and amidophosphite (toluene, 110°C) form the unstable 5-phosphitoindoles **62** (132-124 ppm), which are isolated in the form of thiophosphates **63** (62-64 ppm) [159]:




**62**

**63**

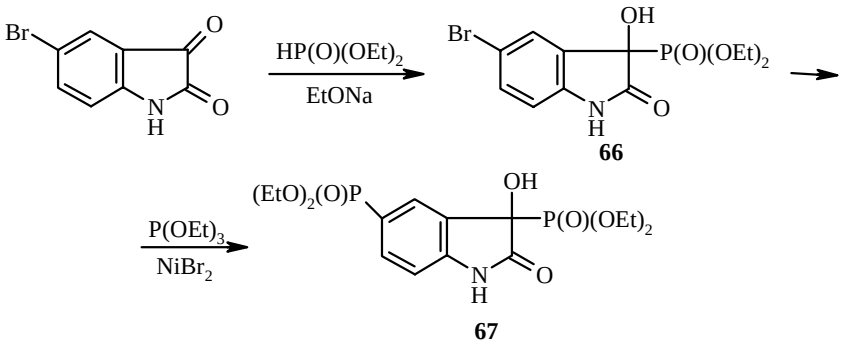
Interesting derivatives of indole were described in [35]. When 3-ethoxycarbonyl-2-methyl-4-(trimethylammonium)methyl-5-hydroxyindole iodide [162, 163] is heated with an excess of trialkyl phosphite [64] (160-165°C, 30 min) 3-ethoxycarbonyl-2-methyl-4,5-(2-oxo-2-alkoxy-1,2-oxaphospholene-4,5)indoles **65** (33-36 ppm) are formed. According to the authors, they are formed from 3-ethoxycarbonyl-5-hydroxy-2-methyl-4-(O,O-dialkylphosphonato)methyleneindoles (**64**):



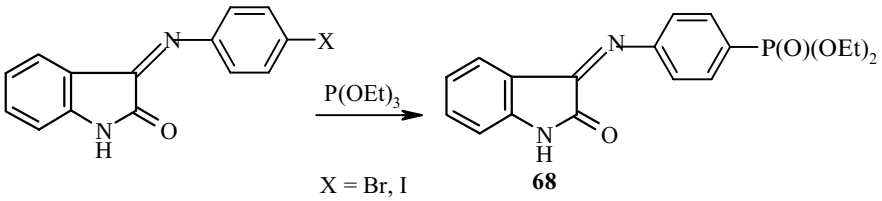

**64**

**65**

In [62] the synthesis of phosphorus-containing derivatives of 2-indolinone was reported. Thus, in 5-bromoisatin one phosphorus-containing fragment was introduced by the Abramov reaction with the formation of compound **66** [233], and a second was then introduced by the Arbuzov reaction (compound **67**):



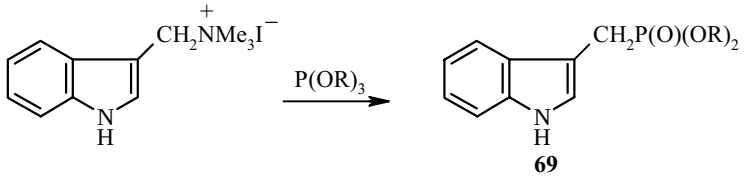
The same paper describes the reaction of trialkyl phosphites with isatin arylazomethines in the presence of nickel or copper monohalides, leading to the previously unknown phosphorus-containing derivatives of 2-indolinone **68**:



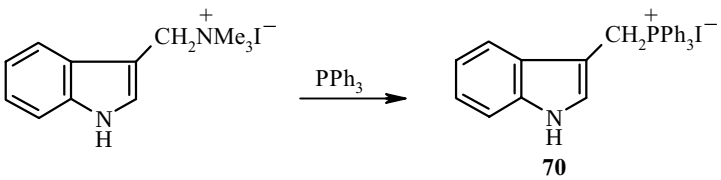
It has been observed [63] that in the presence of *tert*-butyl peroxide trialkyl phosphites phosphorylate the phenyl fragment of the carbazole molecule.

## 2.3. Introduction of Phosphorus-containing Substituent into the Side Chain of Indole and Pyrrole Derivatives

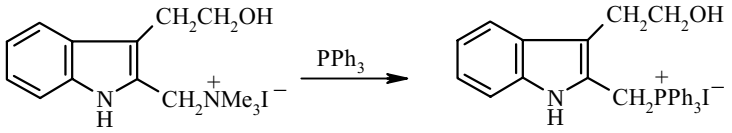
The first publication on the use of phosphites for the synthesis of indoles phosphorylated in the side chain relates to 1957. The authors [64, 65] showed that gramine methiodide reacts with trialkyl phosphites by the Arbuzov reaction with the formation of 3-indolylphosphonates **69**:



3-(ω-Phosphonyl)acylindoles were obtained by a similar scheme [66]. The use of gramine methiodide in reaction with triphenylphosphine and the production of the phosphorus-containing analog of gramine **70** were described in [67]:

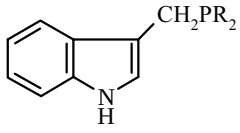


Study of the behavior of triphenylphosphine in reactions with hydroxyl and ammonium groups in derivatives of indole [68] showed that the ammonium group is substituted selectively with the formation of indole **71**.



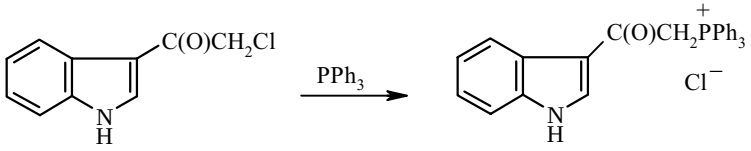
**71**

The dimethylamino group is exchanged comparatively readily by dialkylphosphino group [69] in the reaction of gramine **14** with secondary phosphines, leading to the formation of dialkyl(3-indolylmethyl)phosphines **72**:



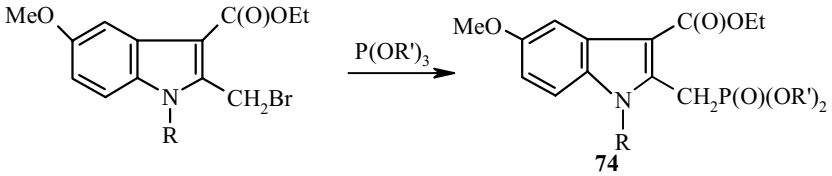
**72**

The reaction of triphenylphosphine with 3-(chloroacetyl)indole [70] led to phosphonium salt **73**:



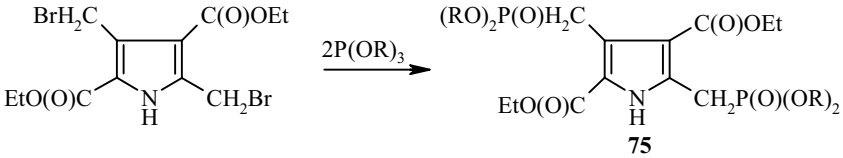
**73**

By means of the Arbuzov reaction the authors of [71] synthesized 2-(alkoxyphosphonyl)methyl-3-ethoxycarbonyl-5-methoxyindoles **74**:



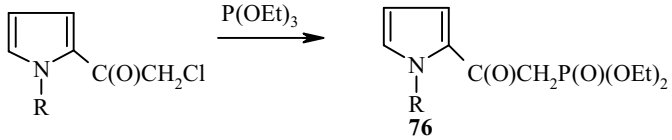
**74**

Phosphorus-containing pyrroles and carbazoles were obtained according to the schemes used for the indole derivatives. Thus, the reaction of 3,5-di(bromomethyl)-2,4-diethoxycarbonylpyrrole [72] with trialkyl phosphites led to 2,4-diethoxycarbonyl-2,5-di(O,O-dialkylphosphonylmethyl)pyrroles **75** [10]:



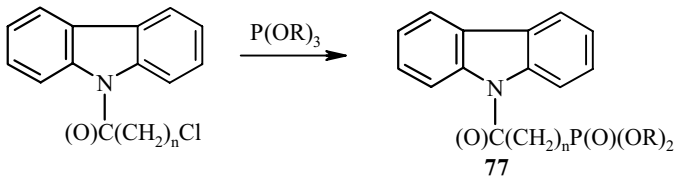
**75**

With triethyl phosphite 2-halogenoacetylpyrroles form O,O-diethyl 2-acetylpyrrylphosphonates **76** [73]:



**76**

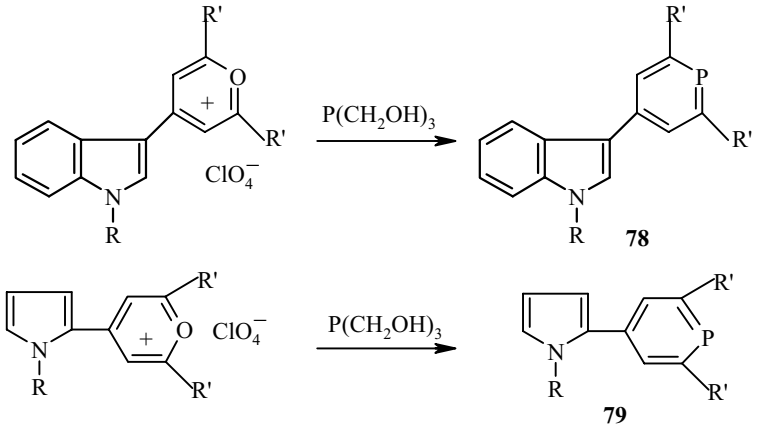
N-ω-(Phosphonyl)acylcarbazoles **77** were synthesized in a similar way [74]:



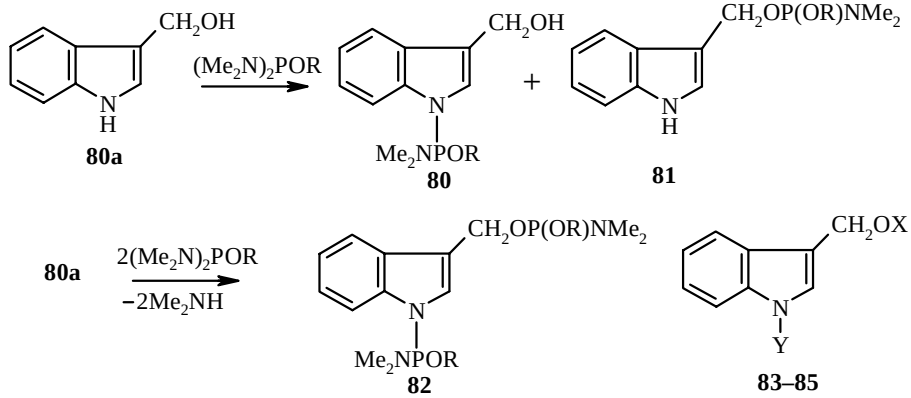

**77**

The reaction of pyrrolidone with triphenyl phosphite and benzaldehyde, leading to 1-(phenyldiphenoxyphosphorylmethyl)-2-pyrrolidone, has been described [75].

The indole (**78**) and pyrrole (**79**) derivatives, containing phosphabenzene with a dicoordinated phosphorus atom as substituent, were obtained [76] in the reaction of indole- and pyrrole-substituted pyrrylium salts with trimethylolphosphine:




In reaction with amidophosphites hydroxymethylindole **80a** gives the N-phosphorylation (**80**) and O-phosphorylation (**81**) products [77]. At -5°C compound **80** is formed preferentially (80-85%); if the temperature is raised to 80°C its fraction amounts to 65-70%, while that of the O-phosphorylation product **81** is 30-35%. With a twofold excess of the amidophosphite instead of equimolar amount it is possible to obtain the diphosphorylated derivatives of 3-methylindole (**82**). All the compounds with a tricoordinated phosphorus atom (**80**-**82**) are easily oxidized in air to the corresponding compounds with a tetracoordinated phosphorus atom (**83**-**85**):

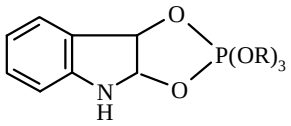



**83** X = H, Y = $Me_2NP(O)(OR)$; **84** X = $P(O)(OR)NMe_2$, Y = H;
**85** X = Y = $P(O)(OR)NMe_2$

## 2.4. Phosphorylation of Carbonyl Group in Derivatives of Indole and Pyrrole

Published data on the reaction of isatin with di- and trialkyl phosphites are somewhat contradictory. In particular, the authors in [78] showed that isatin with trialkyl phosphite forms 2:1 adduct, which has the structure of 1,3,2-dioxaphospholane containing a pentacoordinated phosphorus atom. More recently analogous results were obtained in the reaction of isatin with amidophosphites [79]. At the same time it was shown [80] that 5-methylisatin reacts with trialkyl phosphites with the formation of 3-dialkoxyphosphoryl-3-hydroxy-2-indolinones, identical with the compounds obtained in the reaction of isatin with dialkyl phosphites [78]. In the monograph [4] with reference to the patent [61] the reaction of diethyl phosphite with isatin under the conditions of the Abramov reaction was indicated to lead to 3-dialkoxyphosphoryl-2-indolinone. In all probability this needs verification.

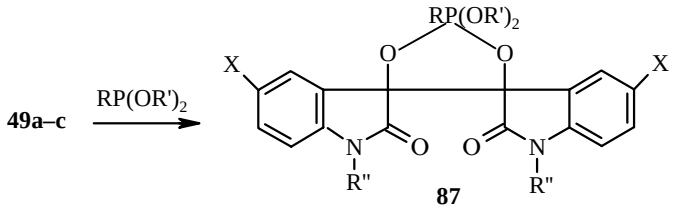
The product from the cycloaddition of trialkyl phosphite to isatin, which the authors [81] assigned the structure **86**, was described as a potential antioxidant:



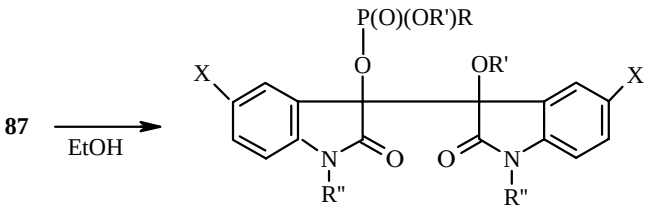

**86**

In the light of [78, 79, 83], however, the structure requires revision.

These published data prompted the authors [82] to undertake a more detailed study of the phosphorylation of isatin by the esters of P(III) acids and hydrophosphoryl compounds. At room temperature in the absence of traces of moisture isatin **49a**, 1-acetylisatin **49b**, and 5-bromoisatin **49c** react with trialkyl phosphites and phosphonites with the formation of the unstable 1,3,2-dioxaphospholanes **87** with a pentacoordinated phosphorus atom, which isomerize in alcohol solution to the stable phosphoryl compounds **88**:

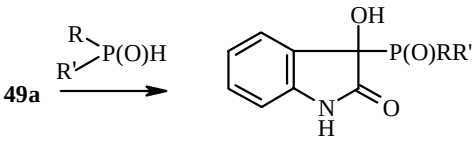



**87**




**88**

In [78, 80] the reaction of isatin **49a** with hydrophosphoryl compounds, realized in the absence of catalyst (in boiling benzene), led to 3-dialkoxyphosphonyl-3-hydroxy-2-indolinones **89**. According to data in [82], with the reagents in a ratio of 1:1 the structure of the final products is not affected by change in the reaction conditions. Thus, phosphonates **89** are obtained after 1 h in the presence of sodium ethoxide in boiling ethanol. These compounds are also produced when the initial reagents are mixed at room temperature for 24 h. In the absence of the catalyst in boiling benzene the reaction time is 8 h. The structure of compound **89** was proved by X-ray diffraction analysis. The indole fragment of the molecule is planar within 0.050(3) Å, and its planarity is determined by conjugation of the unshared electron pair of the nitrogen atom, the $C_{(2)}=O_{(2)}$ bond, and the $\pi$ system of the benzene ring. The data on the bond lengths in this fragment indicate the presence of conjugation. The geometry of the phosphonate fragment of the molecule is usual. In the crystal the molecules of **89** form infinite networks through intermolecular hydrogen bonds $N–H\cdots O_{(1')}$ $(1/2 + x, 1/2 – y, 1/2 + z)$ and $O_{(3)}–H\cdots O_{(2'')}$ $(1 – x, – y, 2 – z)$. The bond parameters are as follows: $N\cdots O_{(1')}$ 2.824(3), N–H 0.77(3), $H\cdots O_{(1')}$ 2.06(3) Å, angle $N–H\cdots O_{(1')}$ 172(3)°; $O_{(3)}\cdots O_{(2'')}$ 2.769(3), $O_{(3)}–H$ 0.85(3), $H\cdots O_{(2'')}$ 2.00(3) Å, angle $O_{(3)}–H\cdots O_{(2'')}$ 150(3)°.

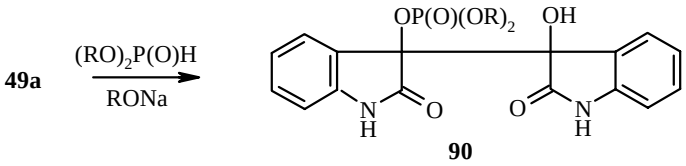


**89a–d**

**89a–d a** R = R'= OMe; **b** R = R' = OEt; **c** R = OH, R' = *p*-$C_6H_4Me$; **d** R = OH, R' = α-naphthyl

An unexpected result was obtained [82, 83] with isatin and dialkyl phosphite in a ratio of 2:1. At room temperature in the presence of sodium alkoxide 3-dialkylphosphoryl-3'-hydroxy-3,3'-di(2-indolinone) **90** is formed. In boiling ethanol with the reagents in the same ratio hydroxyphosphonates **89** were obtained.

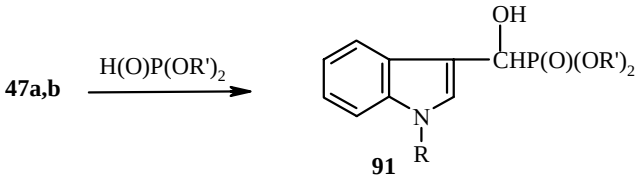
The formation of phosphates **90** can be explained by phosphonate–phosphate rearrangement catalyzed by bases [84]. The authors of [82] were able to show that phosphonates **89** react with isatin (in the presence of sodium alkoxide), leading to compounds **90**.



**90**

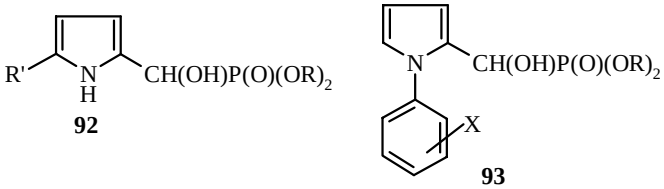
The structure of diindolinone **90** was confirmed by X-ray diffraction analysis.

3-Formylindole **47a** and 1-acetyl-3-formylindole **47b** react with dialkyl phosphites [85, 86] with the formation of 3-(hydroxyphosphonyl)methylindoles (**91**), from which ethers (isopropyl, butyl) and esters (benzoate) were obtained by reaction at the hydroxyl group *via* the alcoholate formation.



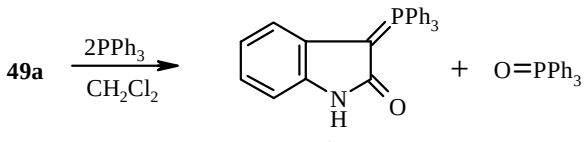
**91**

The phosphorylated derivatives **92** [87] and N-arylpyrroles **93**, having biological activity [88], were synthesized from 2-formylpyrroles:



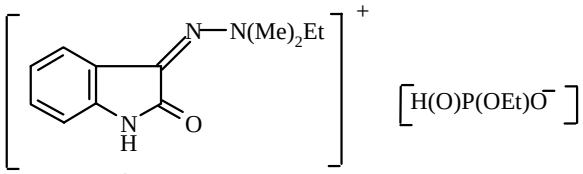
**92** **93**

With a twofold quantity of triphenylphosphine as opposed to an equimolar amount after holding for 20 days isatin **49a** gave 73% yield of the adduct **94** and triphenylphosphine oxide (92%) [73, 89]:



**94**

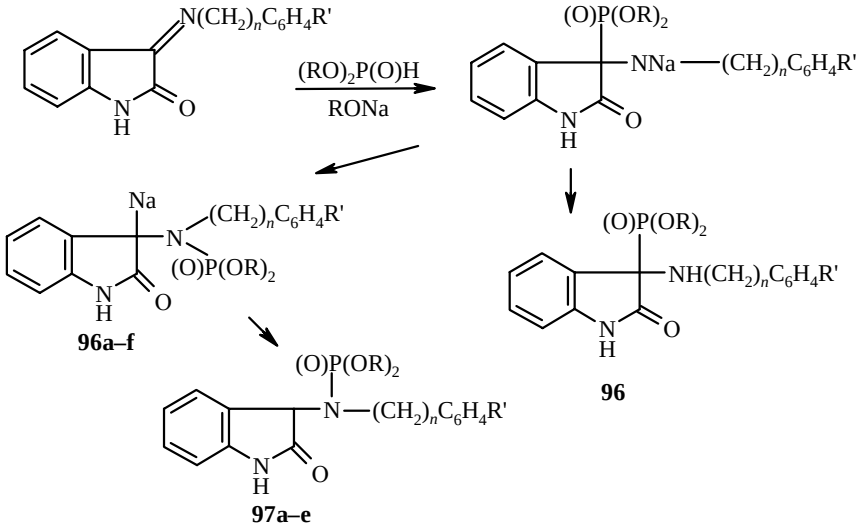
The phosphorylation of isatin azomethines was studied in [90]. The reaction of hydrophosphoryl compounds with Schiff bases was described in the review [91] and the monograph [92]. As a rule, the C=N bond is opened by dialkyl phosphites with the formation of the products of C-phosphorylation. It was noted in [93] that N-phosphorylation occurs if there are some electron-withdrawing groups at the carbon atom in the C=N group. For the case of the reaction of 4-(*p*-dimethylamidoanil)-3-methyl-1-phenylpyrazol-5-one with dimethylphosphorous acid the 1,4-addition, leading to N-phosphorylated compounds, was shown to take place in the conjugated –N=C–C=O system [94]. In the opinion of the authors [95] O-phosphorylation occurs in the case of isatin dimethylhydrazone, although this was not supported by physicochemical investigations. Later the authors reexamined their views and considered that isatin-N-ethyl-N,N-dimethylhydrazonium ethyl phosphite **95** (3.3 ppm) is formed during the reaction of isatin N,N-dimethylhydrazone with diethylphosphorous acid [96].




**95**

The introduction of a phosphorus-containing group into the side chain of the hydrazone fragment of isatin was reported in [97]. The results of a study of the kinetic relationships and mechanism of the addition of dialkyl phosphites to substituted benzylideneamines, which were related to the basicity of the initial amines, were published as abstracts in [98].

The reaction of isatin azomethines with hydrophosphoryl compounds takes place ambiguously [90]. In particular, the formation of only the C-phosphorylated compounds was detected for compounds **96** (R' = $SO_2NH_2$, $n$ = 0; R' = H, $n$ = 1) (according to $^{31}$P NMR data). From the other studied azomethines a mixture of isomeric C- and N-phosphorylated substances was obtained as a result of the reaction. The authors of [90] suggested that hydrophosphoryl compounds react with isatin azomethines according to a scheme including types of 1,2- and 1,4-addition leading to the formation of the C-phosphorylated (**96**) and N-phosphorylated (**97**) derivatives of 2-indolinone respectively. However, according to the refined data [83], the formation of 2-indolinones **96** and **97**, produced as a result of the reaction of isatin azomethines with hydrophosphoryl compounds, is described by the following scheme:




**96a–f**

**96**

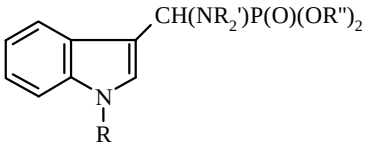
**97a–e**

**96, 97 a** R' =H, $n$ = 0; **b** R'= OMe-*p*, $n$ = 0; **c** R' = COOH-*p*, $n$ = 0; **d** R' = Cl-*p*, $n$ = 1; **e** R' = H, $n$ = 1; **f** R' = $SO_2NH_2$, $n$ = 0; (throughout R = Me, Et)

In the presence of sodium alkoxide an unstable intermediate containing sodium substituent at the nitrogen atom is formed. This is converted into the C-phosphorylated (**96**) or N-phosphorylated (**97**) derivative, in the latter case undergoing a thermal rearrangement under the reaction conditions, and this was confirmed experimentally.

The formation of the products from N-phosphorylation and N-alkylation in a ratio of 6:1 was detected in the reaction of phosphites with N-phosphoryltrifluoroacetylindolylphosphonate [102].

Phosphorylated aminomethylindoles **98** were obtained from 3-formylindoles **97a**,**b**, amines, and hydrophosphoryl compounds [99-101] in the Kabachnik–Fields reaction [233-235]. As shown by DTA, 3-(hydroxyamino)methylindole is formed initially in the case of secondary amines and then it reacts with dialkylphosphorous acid. In the case of ammonia and primary amines imine is formed at the first stage and then it adds dialkylphosphorous acid.

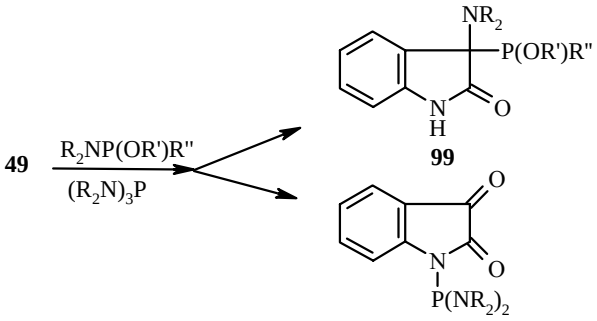



**98a–e**

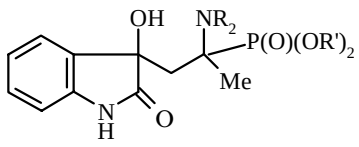
**98 a** R = H, R'= Et, R" = Me; **b** R = H, R' = Et, R" = Et; **c** R = H, R' = Bu, R" = Pr;
**d** R = Ac, R'= Bu, R" = Bu; **e** R = Ac, R' = indolinyl, R" = Et

Analogous compounds are formed in the reaction of 3-formylindole with amidophosphite esters.

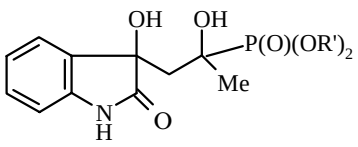
Isatin **49** reacts with amidophosphites with an appreciable exothermic effect [49], 3-amino-3-phosphonato-2-indolinones **99** and 1-amidophosphitoisatins **100** being formed [103].



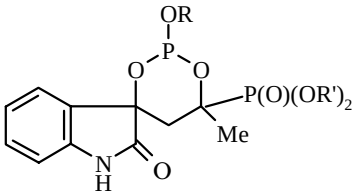

3-Hydroxy-3-(2-oxopropyl)-2-indolinone, synthesized by the condensation of isatin with acetone, enters into the Kabachnik–Fields and Abramov reaction, leading respectively to 3-hydroxy-3-(2-dialkylamino-2-dialkoxyphosphoryl)propyl-2-indolinones **101** and 3-(2-dialkylphosphoryl-2-hydroxypropyl)-3-hydroxy-2-indolinones **102**. The latter react with diamidophosphite ester, leading to the spiro compounds **103** containing the phosphorus atoms in various coordinations, and they are easily transformed into the spiro compounds **104** [104, 105].



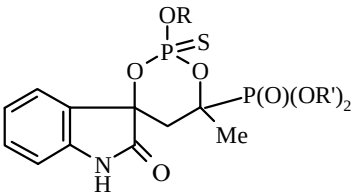

**101**




**102**



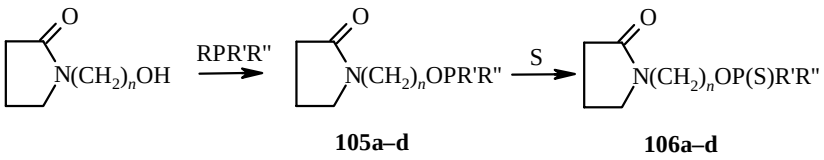

**103**




**104**

## 2.5. Phosphorylation of 2-Pyrrolidone Derivatives

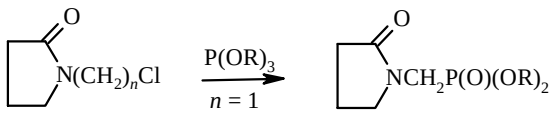
The reaction of 1-hydroxyalkyl-2-pyrrolidones with phosphites, amidophosphites, and chlorophosphites [106] leads to pyrrolidonyl phosphites **105**, which are easily converted into the corresponding thiophosphates **106**:




**105a–d** **106a–d**

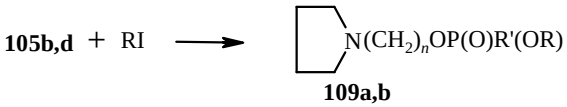
**105, 106 a** R' = R" = OAlk, *n* = 1; **b** R' = R"= OAlk, *n* = 2;
**c** R' = R" = $NAlk_2$, *n* = 2; **d** R' = R" = OAlk, *n* = 3; R = Cl, OAlk, $NAlk_2$

During study of the behavior of 1-chloroalkyl-2-pyrrolidones **107a-c** in reactions with esters of P(III) acids it was shown that the direction of the reaction differs, depending on whether the halogen atom is separated from the nitrogen atom of the heterocycle by one, two, or three methylene groups [107, 108]. 1-Chloromethyl-2-pyrrolidone **107a** reacts with trialkyl phosphites according to the Arbuzov reaction scheme with the formation of 1-(dialkoxyphosphonatomethyl)-2-pyrrolidones **108**. The experimental conditions for the syntheses are similar to the conditions for the reaction of α-chloroamides with trialkyl phosphites [109].




**107a–c** **108**

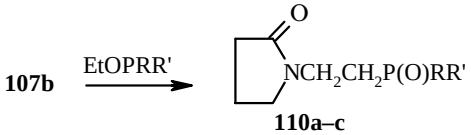
In the case of 1-(2-chloroethyl)- and 1-(3-chloropropyl)-2-pyrrolidones (**107b,c**) significantly more rigorous conditions are required. $^{31}P$ NMR analysis of the high-boiling residue after removal of the excess of trialkyl phosphite indicates a phosphite structure for the obtained compounds **105b**,**d** (138-139 ppm). Chemical evidence for the preservation of the coordination of the P(III) atom in compounds **105b**,**d** is provided by the production of the corresponding phosphonates **109a**,**b** from them by the Arbuzov reaction:




**109a,b**

**109 a** R = Alk, R'= Alk', *n* = 2; **b** R = Alk, R' = Alk', *n* = 3

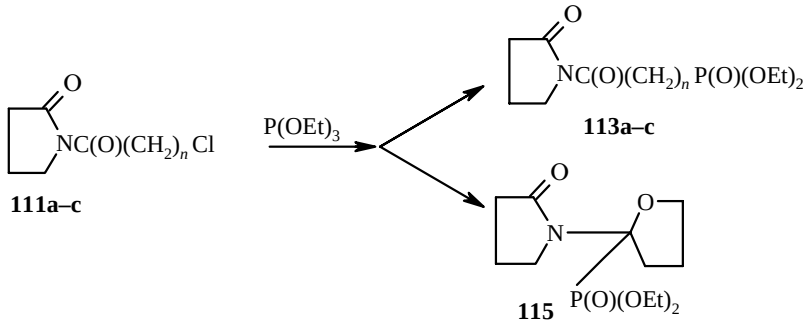
The nature of alkyl halide and the environment of the phosphorus atom make a substantial contribution to the direction of the reaction. Thus, cyclic phosphites [108], like trialkyl phosphites [110], react with preservation of the coordination of the P(III) phosphorus atom (126-132 ppm). If the alkoxyl group is substituted by amide, alkyl, or aryl, the nucleophilicity of the phosphorus atom in the corresponding amidophosphite (phosphonite) increases in comparison with the trialkyl phosphite. This probably promotes attack by 1-haloalkyl-2-pyrrolidone at the phosphorus atom and not the oxygen, and this was confirmed experimentally. As a result of the investigated reactions amidophosphonates or ethyl phenyl phosphinates **110a-c** were isolated; compounds with P(III) were not detected in these cases.



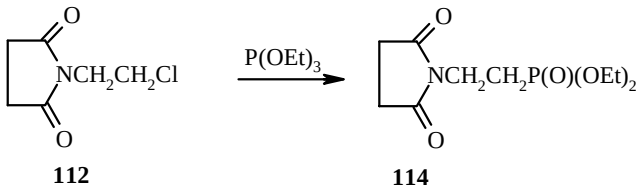

**110a–c**

**110 a** R = R' = $NAlk_2$; **b** R = $NAlk_2$, R' = Et; **c** R = $NAlk_2$, R' = Ph

The authors of [10] studied the behavior of chlorine-containing imides containing pyrrolidone ring in reactions with trialkyl phosphites. It was found that the direction of the reaction depended substantially on the temperature conditions and on the distance between the chlorine atom and the imide fragment. Thus, in the case of N-(chloroacetyl)-2-pyrrolidone (**111a**), N-(3-chloropropionyl)-2-pyrrolidone (**111b**), N-(4-chlorobutyryl)-2-pyrrolidone (**111c**), and N-(2-chloroethyl)-2,5-pyrrolidinedione (**112**) at 140°C phosphonates **113a-c**, **114** are formed:

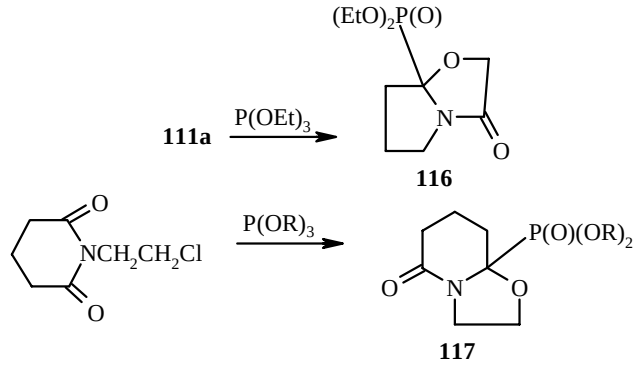



**111**, **113 a** *n* = 1, **b** *n* = 2, **c** *n* = 3




When the temperature was increased to 150°C, phosphorilated oxalanes **115** were isolated in addition to compounds **113**.

By changing the order of mixing of the reagents and increasing the temperature to 160-175°C it is possible to direct the process to the exclusive formation of oxalanes **115** and oxazolidines **116**, **117**:

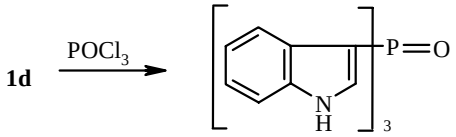



Monophosphorylated and diphosphorylated derivatives of 2-aminopyrroline were synthesized by the direct condensation of aminopyrroline and chlorophosphite [111].

## 3. DERIVATIVES OF INDOLE AND PYRROLE CONTAINING A TETRACOORDINATED PHOSPHORUS ATOM

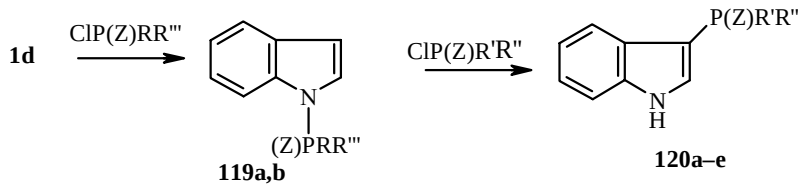
### 3.1. Phosphorylation with Derivatives of P(IV) Acids

In one paper [112] on phosphorylated indoles phosphorus oxychloride was used in reaction with indolylmagnesium halides (**1d**) for the synthesis of tris(3-indolyl)phosphine oxide **118**:



**118**

The indole Grignard reagent (**1d**) was also used for the production of 1-indolyl- (**119**) and 3-indolyl- (**120**) phosphonates and phosphinates [113]:

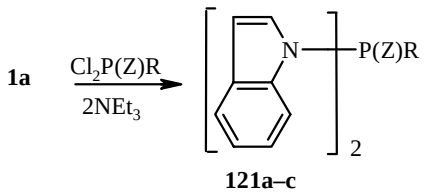


**119a,b** **120a–e**

**119 a** R = R''' = $CH_2Cl$, Z = S; **b** R = R''' = OPh, Z = S. **120 a** R' = Me, R'' = OEt, Z = O; **b** R' = Et, R'' = OEt, Z = O; **c** R' =R'' = OEt, Z = S; **d** R' = CH(OEt)Me, R'' = OEt, Z = O; **e** R' = R'' = Ph; Z = S

In contrast to the derivatives of P(III), the monochlorides of the acids of tetracoordinated phosphorus are less reactive in reaction with indole [44]. Thus, diethyl chlorophosphate reacts with indole when heated at 140-150°C in a sealed ampoule, diphenyl chlorophosphinate reacts at the temperature of boiling toluene, and only bis(chloromethyl)chlorophosphinate reacts at room temperature. Attack by the phosphorus-containing reagent in these cases is directed at the indole nitrogen atom (**119c** R = R''' = $CH_2Cl$, Z = O; **119d** R = R''' = OEt, Z = O; **119e** R = R''' = Ph, Z = O).

In the case of diethyl chlorophosphate 1-ethylindole, the formation of which agrees with data on the alkylating ability of the derivatives of the phosphorus acids, was isolated [114]. In the transition to the dichlorides of P(IV) acids, where the electrophilicity of the phosphorus atom is increased in comparison with the monochlorides, the reaction takes place under milder conditions (at about 0°C) and is accompanied by an insignificant exothermic effect. In the reaction products (**121**) the phosphorus atom is bonded to the nitrogen atom of indole:

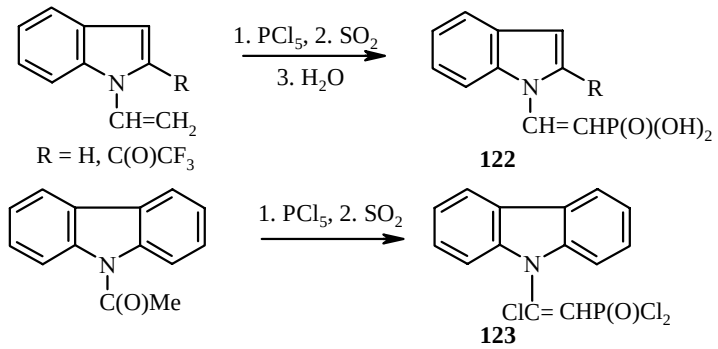


**121a–c**

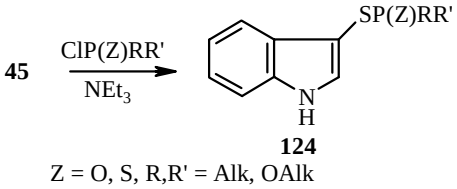
**121 a** R = Me, Z = O; **b** R = $CH_2Cl$, Z = S; **c** R = CH=CHOEt, Z = O

During examination [48, 49, 115, 116] of the reactions of indole with triamidophosphates, diamidomethylphosphonates, amidophosphate esters, and diamidophosphate esters in the opinion of the authors phosphorylation takes place at position 3 of indole in the first two cases only [49].

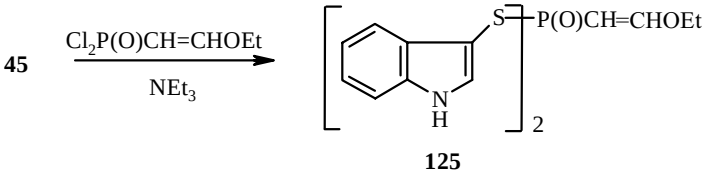
N-Vinylindole and N-acetylcarbazole are converted by successive treatment with phosphorus pentachloride and sulfur dioxide into N-(vinylphosphonato)indoles (**122**) and N-(vinylphosphonato)carbazoles (**123**) [116-119]:



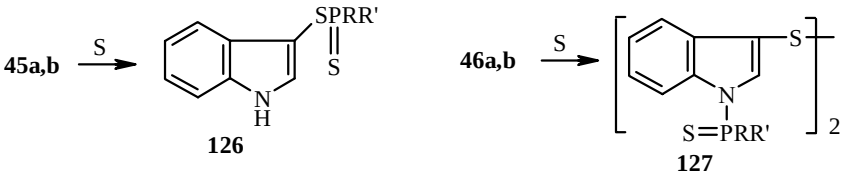

The reaction of 3-mercaptoloindole **45** with the chlorides of the acids of tetracoordinated phosphorus [12] takes place under more rigorous conditions (boiling benzene) than with the derivatives of P(III) acids. According to $^{31}$P NMR and IR spectroscopy, phosphorylation takes place at the sulfur atom with the formation of only one compound **124**.



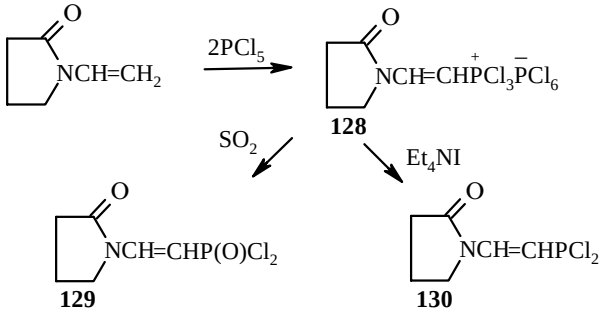

In the transition to the P(IV) acid dichlorides the reaction is conducted under milder conditions (room temperature). However, to increase the yield of compound **125** it is necessary to have a twofold to threefold excess of the base and to remove the precipitated triethylamine hydrochloride periodically from the reaction zone.



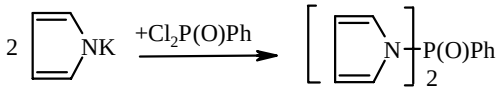

In reaction with elemental sulfur 3-mercaptolophosphitoindoles **45a**,**b** change into the corresponding thiolothiophosphates (thiophosphonates) **126**. In the case of 1-phosphito-3-mercaptoindoles **46a**,**b**, together with the reaction at the P(III) atom, the thiol sulfur is oxidized to disulfide sulfur **127**, which agrees with published data on the ease of the oxidation of thiol sulfur in 3-mercaptoloindole [120].




The phosphorylation of N-vinyllactams with phosphorus pentachloride leads to the formation of the complex **128** and the corresponding dichlorides of phosphonic (**129**) and phosphonous (**130**) acids [121]:

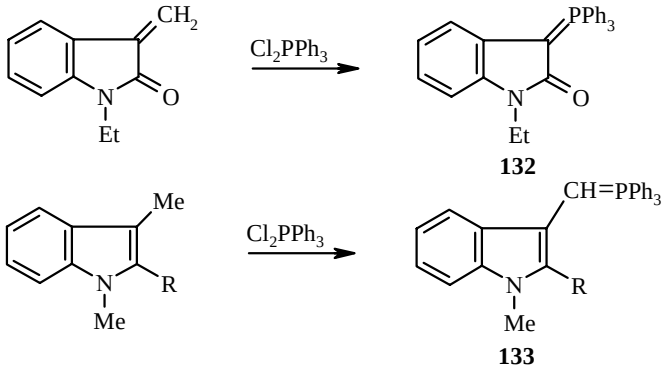


Dichlorophenylphosphine oxide reacts with potassiopyrrole according to N-substitution scheme [122], leading to N,N-dipyrrylphenylphosphine oxide (**131**):



**131**

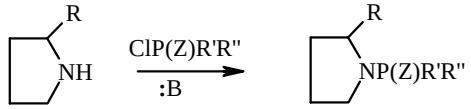
In 1-ethyl-3-methylene-2-indolinone dichlorotriphenylphosphine substitutes the methylene group by a phosphine group with the formation of compound **132** [123], and in di- and trialkylindoles it reacts at the 3-$CH_3$ group with the formation of compound **133** [124]:



**132**

**133**

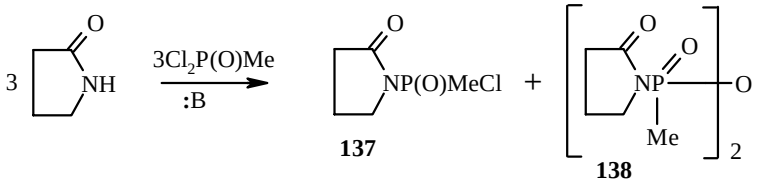
The N-phosphorylated derivatives of pyrrolidine **134** [125, 126], 2-methoxymethylpyrrolidine **135** [127], and 2-ethoxycarbonylpyrrolidine **136** [128] are formed during the reaction of the corresponding heterocycles with mono- and dichlorides of phosphoric, phosphonic, thiophosphoric, and thiophosphonic acids:



**134–136**

**134** Z = S, R',R"= Alk, Ar; **135** Z = O, R = $MeOCH_2$;
R',R" = N-pyrrolidinyl; **136** Z=O; R=C(O)OEt; R'=Cl; R"=OPh

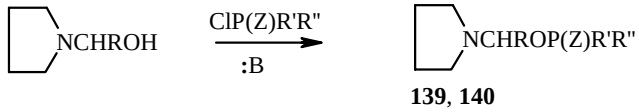
In the reaction of 2-pyrrolidone with equimolar amount of methylphosphonic acid dichloride in absolute ether at -10 to -15°C [129] small yields of (2-pyrrolidonyl)methylphosphonic acid chloride (**137**) and di(2-pyrrolidonyl)dimethylpyrophosphonate (**138**) were obtained:



**137**

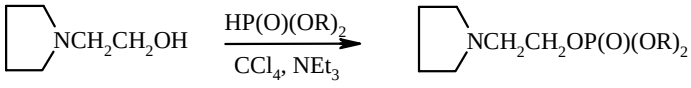
**138**

N-(ω-Hydroxyalkyl)pyrrolidines react at the mobile hydrogen atom of the hydroxy group with the formation of thiophosphonates **139** [130] and phosphates **140** [131, 132] and **141** [133]:



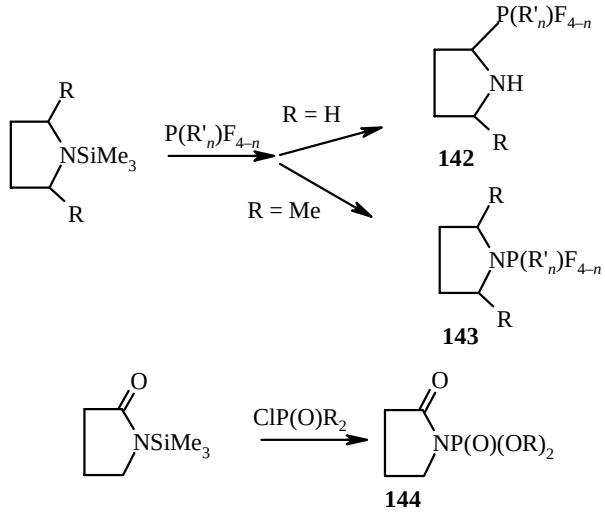

**139**, **140**

**139** Z = S, R = H, R', R" = OAlk, Alk;
**140** Z = O, R = $CCl_3$, R',R" = OAlk, Alk

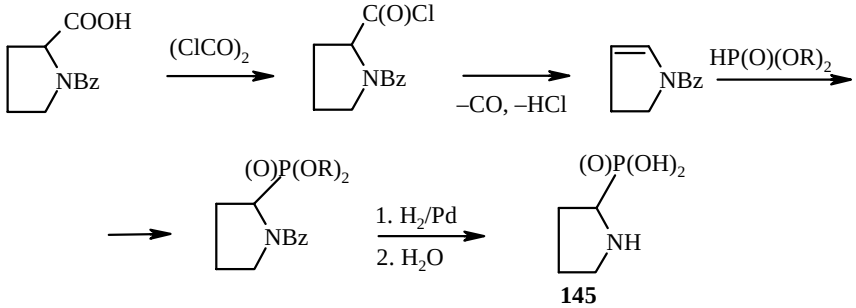



**141** R = Alk

The N-silyl derivatives of alkylpyrrolidine are phosphorylated both at position 2, and at the nitrogen atom with the formation of compounds **142** [134] and **143** [135] respectively, while the analogous derivatives of 2-pyrrolidone react at the nitrogen atom, forming compound **144** [136]:



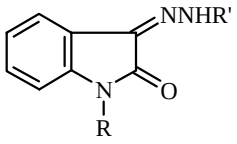

A method for the production of the phosphorus analog of proline **145** has been described [137]:




The authors of [138] propose an one-pot method for the production of disubstituted phosphonous acids that are derivatives of proline.

### 3.2. Phosphorus-containing Analogs of Methisazone

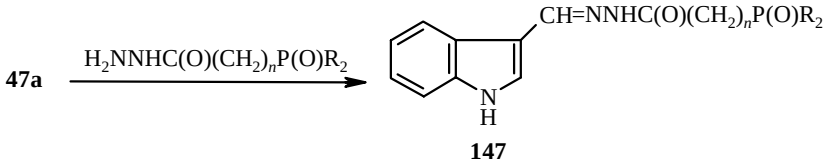
Among biologically active compounds – derivatives of isatin – there is methisazone (1-methylisatin 3-thiosemicarbazone), which has been used as a prophylactic agent against the smallpox virus [139-141]. Methods for the synthesis of compounds with the general formula **146** have been developed in the search for new antiviral and antimicrobial agents [142]:



**146**

**146** R = H; Me; $PPh_3$; $(CH_2)_nP(O)(OEt)_2$; R' = $C(S)NH_2$; $P(S)[NEt_2]_2$

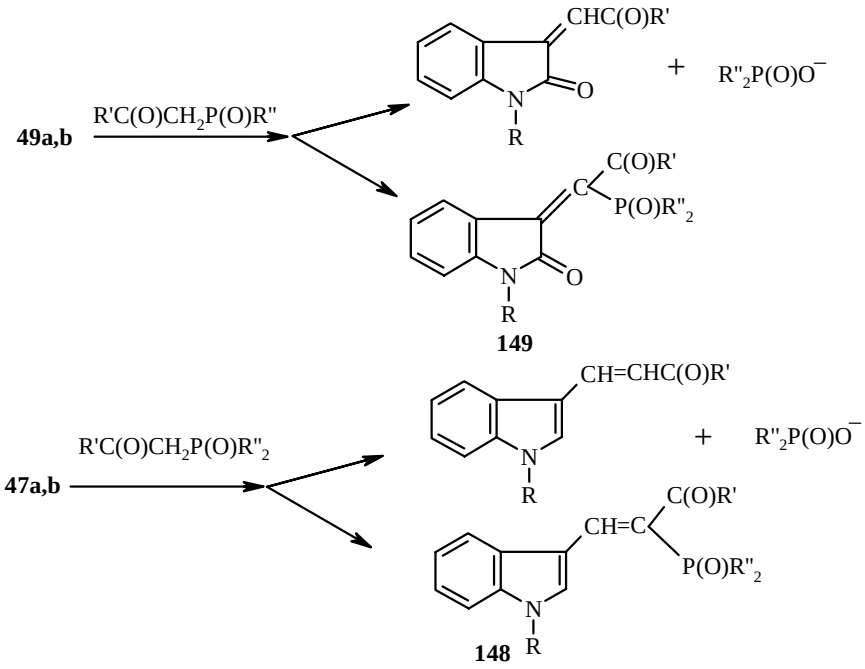
In the search for biologically active compounds a method was proposed [143] for the synthesis of phosphorus-containing hydrazones of 3-formylindole **147**. Here hydrazides of diphenylphosphorylcarboxylic acids, which possess high biological activity [144], were used as phosphorylating agents.



**147**

## 3.3. Synthesis of Phosphorus-containing Indoles Using Organophosphorus Compounds with Active Methylene Group

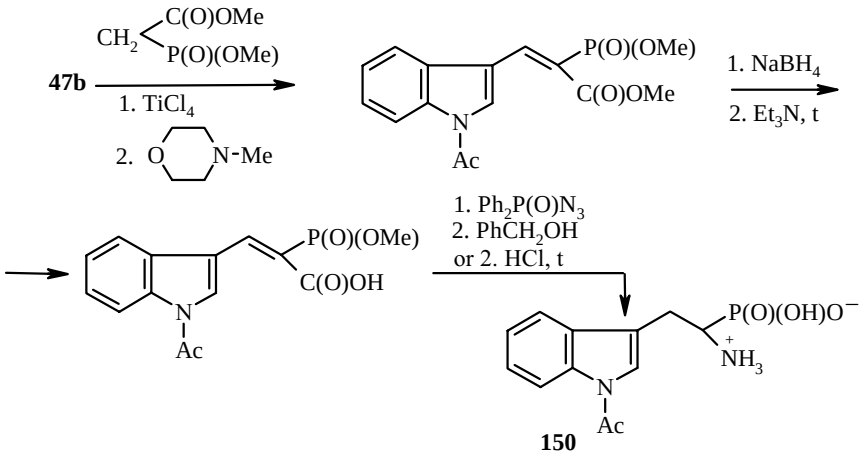
The behavior of 3-formylindoles **47a**,**b** and isatins **49a**,**b** in reactions with organophosphorus compounds containing active methylene group was described in [145-147]. The organophosphorus compounds studied were esters of phosphorylacetic acid, phosphorylacetone, phosphorylacetic aldehyde, phenothiazine containing N-acylphosphoryl group, 2-(phosphorylmethyl)benzimidazole, and 2-(phosphorylmethyl)benzothiazoline. In the case of 1-acetyl-3-formylindole (**47b**), in which the reactivity of the carbonyl group is increased in comparison with that in 3-formylindole on account of the electron-accepting nature of the substituent, the yield of the desired compounds was higher. Together with condensation, leading to the phosphorylated derivatives **148**, **149**, P,O-olefination occurs [148, 149]:



**148, 149** R = H, Ac; R' = H, Me, C(O)Me, C(O)OH, C(O)OEt, N-acylphenothiazine, 2-benzimidazolyl, 2-benzothiazolyl; R″ = Et, OEt, OBu, Ph

The structure of the organophosphorus compound has a considerable effect on the direction of the reaction. Thus, whereas the yield of phosphorus-containing 3-ethenyl-2-indolinones **149** in the case of phosphorylacetic esters amounted to 36-38%, with phosphorylacetone it was possible to isolate 46-48% of the target compounds, but here the process was accompanied by P,O-olefination.

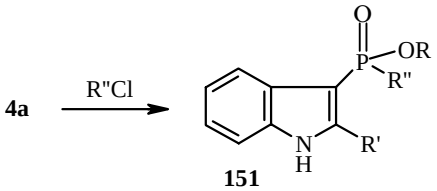
An elegant synthesis of the phosphorus analog of tryptophan **150**, which did not, it is true, exhibit biological activity, was reported in [150]:




**150**

### 3.4. Syntheses of Phosphorus[P(IV)]-containing Indoles Based on Key Compounds with P(III)

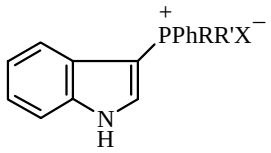
3-Phosphorylated indoles **151** were synthesized from 3-indolylphosphonite **4a** by the Arbuzov reaction [52, 151]:




**151**

**151** R = Et, Pr, *i*-Pr, Bu; R' = H, Me; R" = Et, $CH_2C(O)OR$

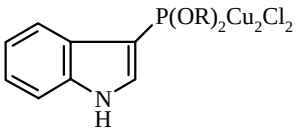
Methods have been developed for the production of quaternary indolylphosphonium derivatives **152** [152]:




**152**

**152** X = Cl, Br, I; R = Me, *i*-Pr, $C_7H_{15}$, $C_8H_{17}$; R' = Ph, 3-Ind

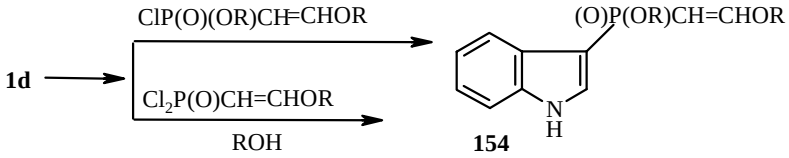
A possibility of obtaining complexes **153** involving P(III)-containing indoles **4a** and copper monohalides has been demonstrated [17]:



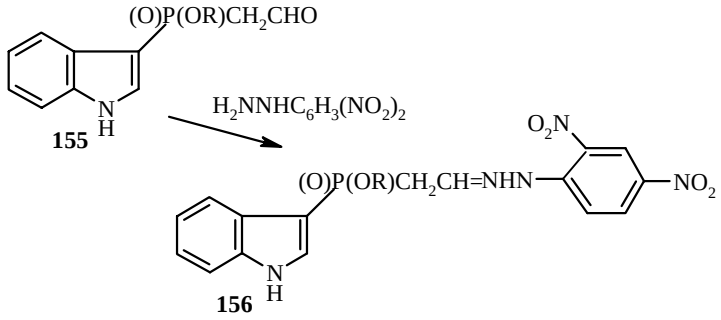

**153**

### 3.5. Transformations in the Side Chain of Phosphorus-containing Indoles

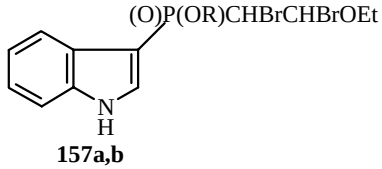
The broad synthetic possibilities of the indole Grignard reagent **1d** have made it possible to synthesize 3-(β-alkoxyvinyl)phosphinatylindoles **154**, which are key compounds for the production of the carbonyl derivatives **155** and arylhydrazones **156** [17, 44]:




Ester chlorides or the readily obtainable chlorophosphonate [84] were used for the synthesis of compounds **154**. Hydrolysis of the compound with a twofold excess of water in the presence of hydrochloric acid in DMF solution led to indolylphosphinatoacetaldehydes **155** [151], identified in the form of 2,4-dinitrophenylhydrazones **156**:



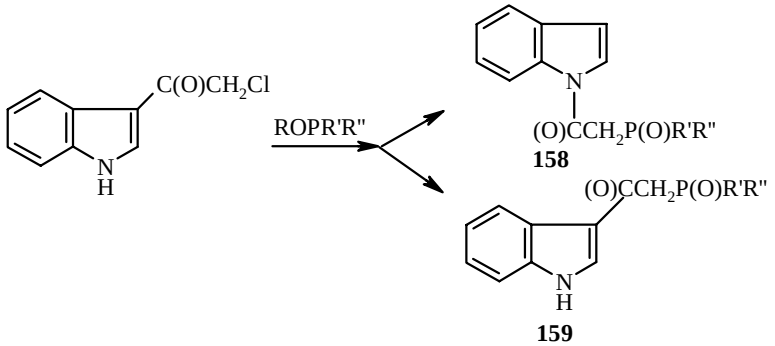

The bromination of compound **154** (carbon tetrachloride, -10 to -15°C) leads to the formation of compound **157**:




**157a,b**

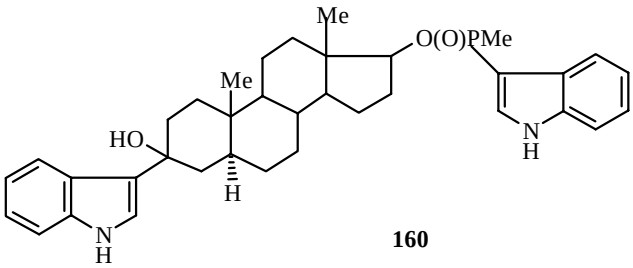
**a** R = Et, **b** R = Pr

In [153] phosphorus-containing acylindoles were regarded as derivatives of natural metabolites. In order to extend the number of such subjects it was proposed [154] to produce 1-phosphorylated (**158**) and 3-phosphorylated (**159**) acylindoles by interaction of chloroacylindoles with esters of P(III) acids according to the Arbuzov reaction scheme. This agrees with published data on the reactions of amides of halogenocarboxylic acids with phosphites [155], since 1-chloroacetylindole can be regarded as such an amide, while 3-chloroacetylindole can be regarded as its vinylog.

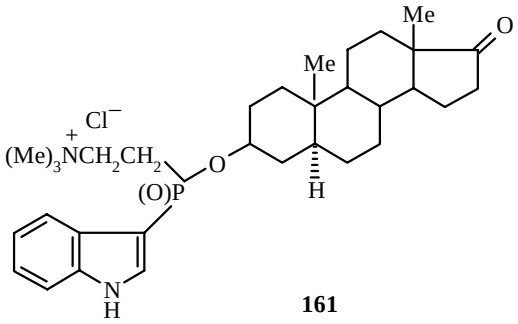


Since the duration of the process is limited by the environment of the phosphorus atom, completion of the reaction in the case of dipropoxyphenylphosphonite required 2.5 h (160-170°C), while in the case of tripropyl phosphite it required 6 h. N-Acetyl(phosphoryl)indole **158** is also produced in the Michaelis–Becker reaction from N-chloroacetylindole and sodium diethyl phosphite [160].

The synthesis of derivatives of steroids dihydrotestosterone **160** and epiandrosterone **161**, containing indole and phosphoryl fragments, is described in the patent [156].



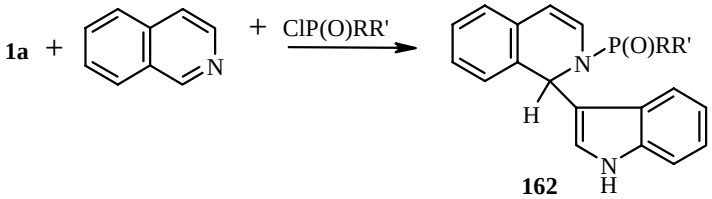

**160**



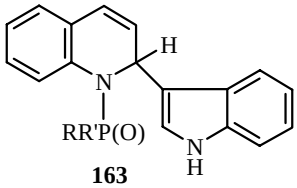

**161**

### 3.6. Phosphorus-containing Heterocyclic Derivatives of Indole

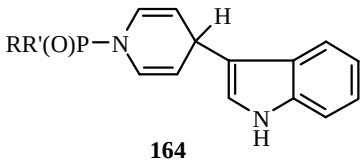
Hetarylation – the direct introduction of heterocycles of aromatic nature into organic compounds – makes it possible to obtain various hetaryl-containing compounds and in particular indole compounds [164]. This method was used for the synthesis of phosphorus-containing heterocyclic derivatives of indole [165-168]. The reactions are realized in a single stage, giving the corresponding derivatives of 3-indolyl-N-phosphorylisoquinoline **162**, 3-indolyl-N-phosphorylquinoline **163**, and 3-indolyl-N-phosphorylpyridine **164**.




**162**




**163**




**164**

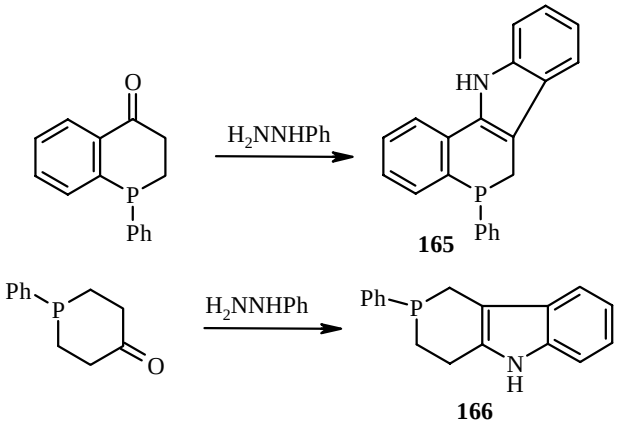
The most reactive in this reaction were N-phosphorylated salts of isoquinoline, which hetarylated indole even at room temperature. Pyridine and particularly quinoline are less reactive. With these heterocycles the reaction took place only in the presence of the more active dialkylphosphinic acid chlorides. The steric effects of the substituents at the phosphorus atom have a definite role. It was found that substituents with smaller molecular mass and less branched substituents made it possible to conduct the reaction under milder conditions and lead to an

increase in the yield of the required products [167]. The most suitable solvent for hetarylation was benzene. Alkaline hydrolysis of compound **162** leads to total fragmentation of the molecule with the formation of isoquinoline, indole, and dialkylphosphoric (phosphinic) acid.

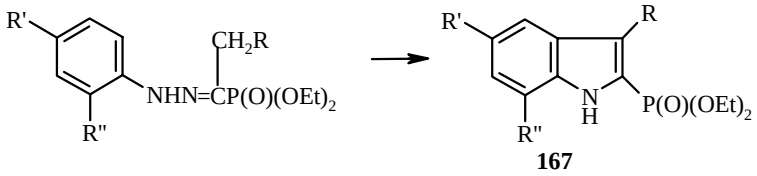
## 4. CYCLIZATIONS IN THE SYNTHESIS OF PHOSPHORUS-CONTAINING INDOLES AND PYRROLES

The use of arylhydrazones for the synthesis of indoles has been widely discussed in the literature [1, 2, 169]. One of the most useable methods is the Fischer reaction [169, 170, 171], modified by Arbuzov [172].

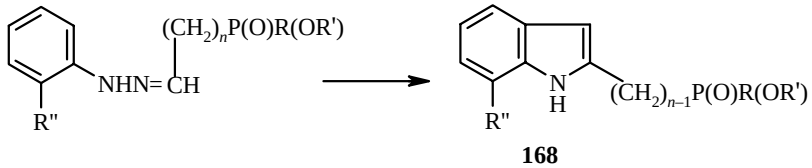
The first publication [173] on the production of phosphorus-containing indoloquinolines **165** by cyclization relates to 1963. Phosphorus-containing carbazoles **166** were obtained in a similar way [174].




Arylhydrazones containing diethoxyphosphoryl group cyclize to 2-phosphorylindoles **167** according to the scheme of the Fischer reaction [175]:

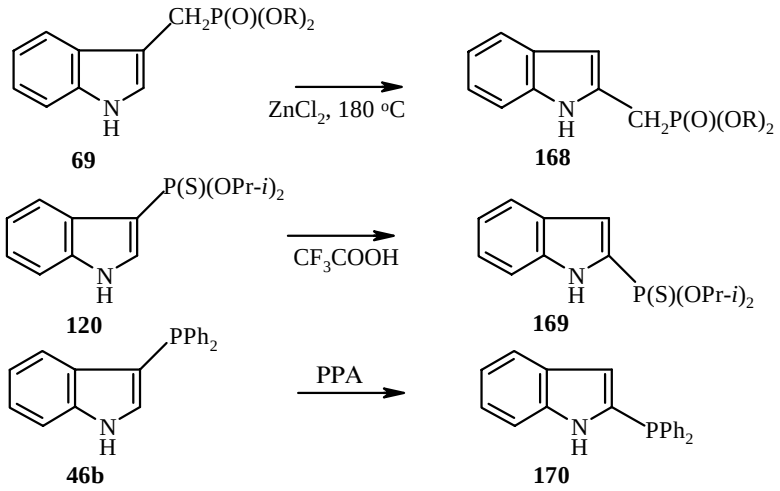



On the basis of phosphorylated acetals and aldehydes [176] it was proposed [177-179] to produce indoles **168** and phosphorylated derivatives of tryptophan [44].

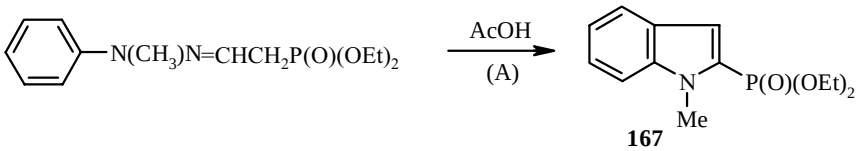



The cyclization of the phosphorylated arylhydrazones, leading to compounds **168**, presumably takes place through the initial formation of 3-phosphorylated indoles **69**, which isomerize to compounds **168** in the course of the reaction. Such 3→2 rearrangements are well-known [30, 180-182, 231]. The transposition of the phosphorus-containing substituent in indoles was first observed in [178, 179]. In the review [8] the data on the formation of 2-phosphorylindoles from the arylhydrazones of phosphorylpropionic aldehyde were considered proved, but the results on the cyclization of hydrazones of phosphorylacetaldehyde to the 2-isomers were placed under some doubt.

Experimental evidence for the possibility of 3→2 migration in the case of compounds with $C_{(3)ind}$–$CH_2P(IV)$ (**69** → **168**), $C_{(3)}$–P(IV) (**120** → **169**), and $C_{(3)}$–P(III) (**4b** → **170**) bonds was obtained in order to resolve this question [44].

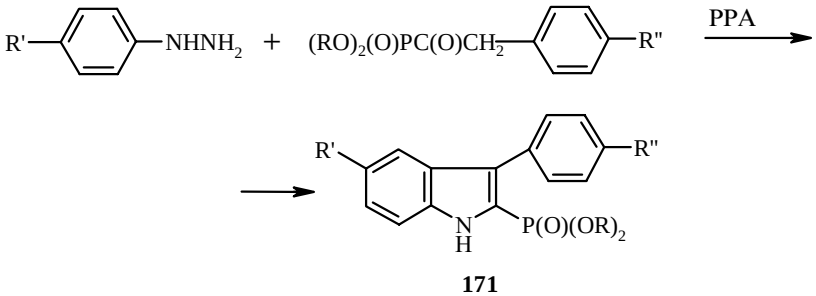



To confirm the scheme with 3→2 migration of the phosphoryl substituent 2-ethoxyphosphorylindole **167** was synthesized [44] by the cyclization of diethoxyphosphorylacetaldehyde N-methylphenylhydrazone in glacial acetic acid (path A) and by the oxidation of 1-methyl-2-diethoxyphosphonitoindole (**3f**, Y = Me, $R^4$ = H, $R^5$ = $P(OEt)_2$) with peracetic acid (path B):




The $^1$H NMR spectra of indoles **167** obtained by the two methods (A and B) were identical.

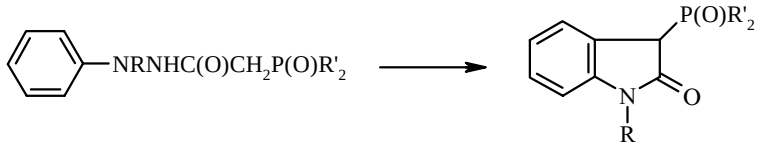
The synthesis of dialkyl 3-aryl-2-indolylphosphonates **171** by the Fischer indole synthesis by the cycloaddition of arylhydrazines with α-ketophosphonates in polyphosphoric acid or under the influence of zinc chloride was described [183]:




**171**

A method was proposed for the production of 2-diphenylphosphino-3-hydroxy-, 3-amino-2-diphenylphosphino-, and 3-alkyl-2-diphenylphosphinoindoles [184].

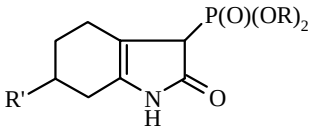
A method was developed [185, 186] for the production of phosphorilated indolinones **172** by the cyclization of arylhydrazides of phosphorylated carboxylic acids. Depending on the conditions, the carboxylic acid arylhydrazides undergo cyclization to various products. Under the harsh conditions of the Brunner reaction (CaO, 200°C) 2-oxoindoles are formed; under the mild conditions of the Kost reaction ($POCl_3$, benzene, 80°C) 2-aminoindoles are formed [187].




R = H, Me; R' = Et, OPr-*i*, Ph **172**

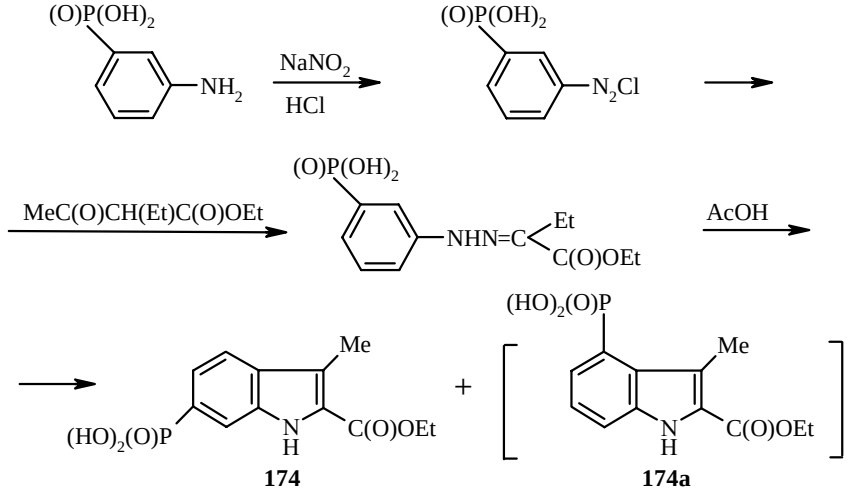
In the case of the arylhydrazides of phosphorylated carboxylic acids variation of the reaction conditions does not affect the structure of the final products; indolinones **172** are formed under the conditions of the Kost reaction and under the conditions of the Brunner reaction.

The reaction of dialkyl phosphites with *p*-substituted nitrostyrenes gave a mixture of 1-HO-2-R"-3-[$(RO)_2P(O)$]-6-R'- indole (R = Et, Pr, *i*-Pr, Bu; R' = H, OMe; R" = H, Me) and 3-phosphorylated tetrahydro-2-indolinone **173** [188]:




**173**

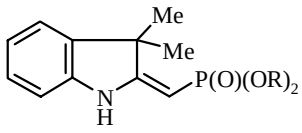
It was proposed to synthesize 6-phosphorylated indoles **174** [189] by the Japp-Klingemann reaction. Diazotization of *m*-(dihydroxyphosphoryl)aniline followed by the reaction of the diazo compound with ethylacetoacetic ester gave *m*-phosphorylphenylhydrazone of ethyl α-ketobutyrate, which was used for the synthesis of the desired compound **174**.




**174** **174a**

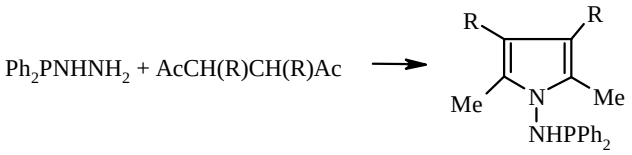
It should be noted that the cyclization of hydrazone could lead to the formation of 6- and 4-phosphorus-containing indoles **174** and **174a**. However, the latter were not found in the reaction mixture, which is probably due to the steric factor. (The bulky phosphoryl group prevents cyclization at the *o*-position to it.) The cyclization of ethyl α-ketobutyrate *o*-phosphorylphenylhydrazone, obtained from *o*-phosphorylaniline by the method in [190], takes place in a somewhat unusual manner. When hydrazone is heated in ethylene glycol (or glacial acetic acid), 2-ethoxycarbonyl-3-methylindole is formed in both cases instead of the expected 2-ethoxycarbonyl-3-methyl-7-phosphonatoindole. In the $^{31}P$ NMR spectrum of the reaction mass there is a signal (0 ppm) characteristic of phosphoric acid, formed as a result of the dephosphorylation of hydrazone in the course of cyclization. The deactivating effect of electron-withdrawing substituents in the aromatic ring on the formation of the indole system has been mentioned [191].

The reaction of enallene phosphonates with phenylhydrazines is accompanied by intramolecular cyclization, leading to the formation of indoline phosphonates **175** [192]:



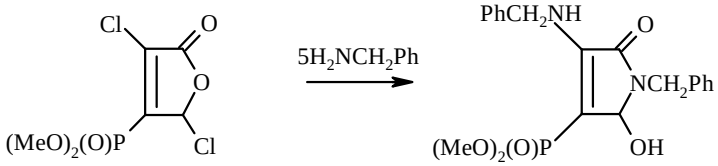

**175**

Several publications have been devoted to the synthesis of phosphorylated derivatives of pyrrole by cyclization and condensation reactions. Diphenylphosphinylaminopyrroles **176** were obtained [193] by the cyclization of dicarbonyl compounds in the presence of diphenylphosphinous acid hydrazide:




**176**

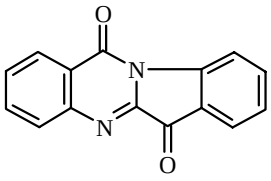
The reaction of 3,5-dichloro-4-dimethoxyphosphoryl-2(5H)-furanone **177** with a fivefold excess of benzylamine under mild conditions in acetonitrile solution gave N-benzyl-3-benzylamino-4-dimethoxyphosphoryl-5-hydroxy-2-pyrrolinone **178** (15.5 ppm) [194, 195]:




**177** **178**

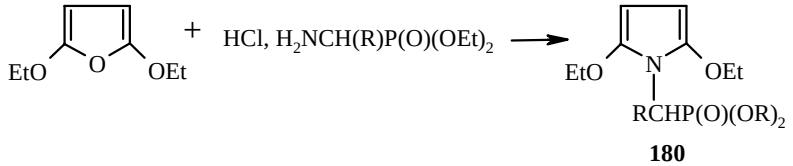
A method was proposed [196] for the production of 4-phosphazenyl-2,3-dihydropyrrol-2-ones and 5-phosphazenyl-2-pyridones from β-(N-acylphosphazenyl)enamines of dimethyl acetylenedicarboxylate. The authors of [197] examined the chemoselective cycloaddition of C-aryl-N-phenyl nitrones at the 1,2 double bond of allenylphosphonates, leading to a mixture of adducts possessing pyrrolidine and isoxazolidine structures.

A highly effective method has been proposed for the synthesis of 6,12-dihydro-6,12-dioxoindolo[2,1-*b*]-quinazoline (**179**) – the alkaloid couropitine A (from the tropical tree *Couropita guianensis*), having the same structure as the antibiotic tryptanthrin (from the yeast *Candida lipolytica* Hegolus), by the reaction of isatin with phosphorus oxychloride followed by treatment of the reaction mixture with ice [198]:



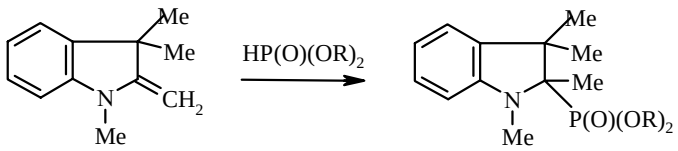

**179**

An example of the transformation of a furan derivative into pyrrole **180** with the participation of aminophosphonate was given in [199]:




**180**

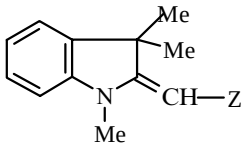
The addition of dialkyl phosphites at the C=C bond of 1,3,3-trimethyl-2-methyleneindoline, leading to 1,2,3,3-tetramethyl-2-phosphorylindolines **181** was described in [31, 193]:




**181**

The new heterocyclic system of 2H-1,3,2-oxaazaphosphorino[6,5-*b*]pyrido[2',3'-*b*]indoles was obtained [200].

The intramolecular interactions in 1,3,3-trimethyl-2-methyleneindolines **182**, containing various groups with tri- and tetracoordinated phosphorus atom in the exomethylene group, were studied by IR and UV spectroscopy [201].




**182**

Z = $PX_2$, $P(Y)X_2$, $P^+(Cl)(NEt_2)_2Cl$; X = Alk, OAlk, $NAlk_2$, Ph, Cl, Br; Y = O, S, NPh

## 5. BIOLOGICAL ACTIVITY OF PHOSPHORUS-CONTAINING DERIVATIVES OF INDOLE AND PYRROLE

A controlled synthesis of biologically active compounds is impossible without studying the relation between the chemical structure and the biological activity. The choice of the necessary type of compound can be approached on the basis of analogies in structure with known biologically active compounds. The initial selection, connected with the need to study a large number of compounds synthesized for the first time, remains significant.

Data on the biological activity of indole and pyrrole derivatives are given in the monographs [1, 2, 4, 196, 197] and in a series of reviews [199, 202, 203]. While summarizing investigations in the region of quantum biochemistry, the authors of [204] mention that the electron-donating activity increases in the order pyrrole–indole–tryptophan–serotonin. This agrees with the fact, mentioned in [205], that the physiological activity of compounds containing indole ring is associated with their electron-donating capacity.

Data on the biological activity of the organophosphorus derivatives of indole and pyrrole are few. The most widely discussed is the question [206, 207] concerning psilocybin – 3-[2-(dimethylamino)ethyl]-4-indolyl dihydrogen phosphate, which gives rise to mobile hallucinations in man at doses of 0.08 mg/kg. The authors of [5] obtained all the possible isomers of psilocybin, which did not exhibit high biological activity. Studies of the fungicidal, insecticidal, and acaricidal activity of 1-indolyl amidophosphates and carbazole derivatives showed that it was lower than in many of the compounds used for these purposes [208, 209]. According to data in [65], 3-indolyl phosphonate and its salts were antagonists of heteroauxins. O,O-Dialkyl skatylphosphonates were regarded as analogs of natural metabolites [210]. Low serotonin-like activity and the absence of cholinomimetic activity were found during study of the biological activity of 5-phosphorylindoles [211], diethyleneimides of 3-indolylalkylamides of phosphoric and thiophosphoric acids [212, 213], and O-phosphate esters of serotonin [61]. Questions of the phosphatase activity of 3-indolyl- and 5-bromo-3-indolylphosphates were elucidated in [214]. 5-Bromo-4-chloro-3-indolyl phosphate was discovered in biochemical substrates [215]. It was observed [216] that the structure of streptomycin metabolite contains tryptophan and phosphate groupings. Data are presented on the

toxicity of phosphorus-containing carbazoles for warm-blooded animals [74]. The authors of [217, 218, 233] found that tryptophan derivatives phosphorylated in the amide group have moderate antitumor activity, while diphosphorylated aminoskatoles have weak antiviral activity (on $A_2$ and B viruses). 2-(Thiophosphato)methylpyrrolidine was tested as a radioprotective agent but did not exhibit activity [158]. Monosodium *L*-2-pyrrolidinylmethyl thiophosphate and its derivatives showed moderate antiradiation activity when tested on mice [219].

The general insecticidal activity of phosphorus-containing pyrrolidine derivatives was mentioned in [125, 126, 133, 220, 221].

Repellent activity was detected in ethers containing pyrrolidine ring in the radical [222, 223]. During initial trials N-pyrrolidylglycolphosphorous acids exhibited weak antifungal activity against dermatophytes and insecticidal and fungicidal activity.

A depressant effect on the central nervous system and an antispasmodic effect was found in the case of 2-oxo-2-pyrrolidino-1,3,2-dioxaphospholanes and phosphorinanes [225, 226].

The antimicrobial activity of amidophosphorylskatoles [49, 103, 115], alkyl 3-indolylphosphinic and phosphonic acid esters [151], 2-oxo-3-phosphorylated indoles [178], phosphorylated hydrazones of isatin [142], phosphorylated (hydroxy)3-methylindoles [227], 3-indolylthiophosphonic acid esters [151], 2-indolinylphosphonates [151], 5-phosphorylated indolines [35], 5-nitro-6-phosphorylindolines [35], 1,3-diindolylthiophosphinates [11], and 1-aryl-2-hydroxy-2-phosphorylpyrroles [88] toward meningococci, streptococci, staphylococci, and the intestinal group of microbes was studied. Analysis of the results of trials of antimicrobial activity [44] showed that it increases in the transition from amides to esters of indolylphosphonic acids. The activity increases when the alkoxy group is replaced by alkyl.

Compounds with antiviral activity have been found among the thiophosphorylated hydrazides of isatin [49].

1-Dialkoxythiophosphoryl-2-pyrrolidones exhibit insecticidal activity at the level of chlorophos and aphicidal and acaricidal activity at the level of carbophos [88, 228].

The synthesis of dinucleotide boranephosphates using chiral intermediates (indoleoxazaphosphorines) was reported recently [229].

The effect of the phosphorus level, interculture, and indolyl-3-acetoacetic acid on the growth and nodulation in *Phaseolus-Radiatus* was described in [230].

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